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EDITORIAL

Updated WFSBP Guidelines for the Biological Treatment of Unipolar Depressive Disorders in Primary Care

In this volume of *The World Journal of Biological Psychiatry* you will find an updated version of the WFSBP Guidelines for the Biological Treatment of Unipolar Depressive Disorders, specifically designed for colleagues working in primary care. These guidelines provide a comprehensive but concise manual for general practitioners and include recommendations for when to seek the help of specialists.

The philosophy behind the WFSBP treatment guidelines is to overcome national divergences and to provide a guide that is accepted by the professional community in countries with diverse psychosocial and economic backgrounds. A Task Force was set up with members of all societies of biological psychiatry affiliated with the WFSBP. I thank the 53 members of the Task Force on Unipolar Depression Disorders for their expertise, their co-operation and for the time they generously spent commenting on several drafts. Other guidelines produced by the WFSBP can be accessed via <http://www.wfsbp.org/guides.html>.

The treatment of depression characteristically involves a multi-professional team including primary care and specialised experts as well as co-workers supporting the patient within his or her social network. All team partners need expertise, empathy for the patient and their family and friends and the ability to interact closely with other professionals over long periods of time.

The general practitioner plays a central role in this network. The majority of patients with depression are treated in the primary care setting and are never or only occasionally seen by specialists. The general practitioner is also the person who accompanies the patient on a long-term basis and gets to know his or her needs, preferences and resources. If the importance of this role was sometimes not fully appreciated, awareness of it has increased with growing knowledge about the life-long, devastating course of the illness and the efficacy of primary care treatment approaches.

We know of the constant challenge of balancing recommendations from textbooks, experts or professional organizations with patients' individual characteristics, situations and preferences as well as with limited resources. With the development of specifically designed versions of evidence-based consensus guidelines, the WFSBP seeks to meet the needs of target professional groups and stimulate a fruitful dialogue about how best to care for our patients. However, the data acquired in randomized controlled trials, which form the main basis of evidence-based recommendation, can only be generalized to a limited extent. With the growing number of practical trials conducted in every-day practice, this gap will hopefully be bridged in the near future.

Despite the necessity for brevity, at some points we decided to include short paragraphs with specialised treatment options in order to provide the users with knowledge of further treatment possibilities so that they can inform patients' decision to seek specialised help. We encourage all readers to share with us their experiences and suggestions for adjustments.

In hope of your co-operation in advancing the care for patients with depression,

Michael Bauer
Chair of the WFSBP Task Force on Unipolar Depressive Disorders

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REVIEW

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care

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Abstract

These practical guidelines for the biological treatment of unipolar depressive disorders in primary care settings were developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). They embody the results of a systematic review of all available clinical and scientific evidence pertaining to the treatment of unipolar depressive disorders and offer practical recommendations for general practitioners encountering patients with these conditions. The guidelines cover disease definition, classification, epidemiology and course of unipolar depressive disorders, and the principles of management in the acute, continuation and maintenance phase. They deal primarily with biological treatment (including antidepressants, other psychopharmacological and hormonal medications, electroconvulsive therapy, light therapy).

Key words: Major depressive disorder, acute treatment, continuation treatment, maintenance treatment, evidence-based guidelines, biological treatment, pharmacotherapy, antidepressants

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Executive summary of recommendations*General recommendations*

For patients who meet the diagnostic criteria for a depressive episode (ICD-10) or a major depressive disorder (DSM-IV), biological treatment (pharmacological and non-pharmacological approaches) should in general be considered. Before treatment is begun, a comprehensive treatment plan should be developed on the basis of the patient's history and experience with previous treatments, current clinical subtype, current findings, severity of illness and risk of suicide. Concurrent psychiatric and somatic disorders, non-psychiatric medications or psychosocial stress factors should be thoroughly considered,

as they can contribute to a depressive syndrome or interfere with treatment. Family history for mood disorders should be assessed. Whichever biological treatment intervention is chosen, clinical and psychiatric management should be initiated and continued throughout the treatment. This includes determining treatment plan and setting, establishing and maintaining a therapeutic alliance, monitoring and reassessing psychiatric status including risk of suicide, reassessing the adequacy of the diagnosis, monitoring the patient's treatment response, side effects and general medical condition, and educating patients and families as to the importance of adhering to treatment. The ultimate goal of the acute treatment phase is remission. After a period of about

2–4 weeks of antidepressant treatment response should be evaluated and, if insufficient, optimization strategies should be implemented. At least 8–10 weeks may be required to define the full extent of symptom reduction which must be achieved before entering the continuation phase of treatment. The more severe the depression is, the greater are the potential benefits derived from adequate treatment. The goal of continuation treatment is to prevent a relapse, to eliminate any residual symptoms and to restore the patient's prior level of psychosocial and occupational functioning. Maintenance (prophylactic) treatment is aimed at preventing a new episode of depression and suicide, and is definitely indicated in situations in which the risk of recurrence is high, i.e. for patients who have had three or more episodes of major depression and in patients with a high prior frequency of recurrences (e.g., two episodes within 5 years). Maintenance treatment may last from 3 years to a lifetime. In general, the graver the prognosis, the longer the maintenance therapy should last. Successful treatment of depressed patients with antidepressants includes educating the patients and the families about available treatment options, time of first noticeable response, early side effects and what to do about them, and the expected course of treatment.

Biological treatment recommendations

Antidepressants are the first-line treatments for a major depressive episode (moderate to severe depressive episode). Depending on individual characteristics and/or requests of the patient, antidepressant treatment might also be indicated in mild depressive episodes, otherwise psycho- and socio-therapeutic approaches alone may be sufficient.

Factors to take into account when choosing an antidepressant are: the patient's prior experience with medication (response, tolerability, adverse effects), concurrent medical conditions and use of nonpsychiatric drugs, a drug's short- and long-term side effects, the physician's own experience with the medication, the patient's history of adherence to medication, history of first-degree relatives responding to a medication, patient preferences, and the costs and availability of specific antidepressants.

No one class of antidepressants has proved to be more effective or have a more rapid onset than another, although some tricyclic antidepressants (TCAs) (amitriptyline and clomipramine), and venlafaxine are slightly more effective than SSRIs in severely depressed hospitalized patients. Antidepressants differ considerably in their side effects profile, potential for interacting with other drugs and in the danger they pose when taken in overdose. Second-

generation (e.g., bupropion, maprotiline, mianserin, trazodone) and third-generation (e.g., SSRIs, SNRIs, mirtazapine and reboxetine) ("newer") antidepressants are generally tolerated better than are the first-generation ("older") TCAs, and patients are thus less likely to discontinue them.

In at least 30% of depressive episodes, patients will not respond sufficiently to an adequately performed first-line treatment with any chosen antidepressant. This situation warrants a careful review of the correctness of diagnosis and sufficiency of drug dosing and compliance. Following this, potential strategies are (1) switching to another antidepressant from a different pharmacological class, (2) switching to another antidepressant within the same pharmacological class, (3) combining two antidepressants from different classes, (4) augmenting the antidepressant with other agents (e.g., lithium, thyroid hormone, pindolol, estrogen, buspirone, atypical antipsychotics) to enhance antidepressant efficacy, and (5) combining the antidepressant with a psychotherapeutic intervention. Of these alternatives, augmentation with lithium is the foremost and best documented strategy.

Electroconvulsive therapy (ECT) should be considered as a first-line strategy only in special situations calling for rapid relief from depression (e.g., severe psychotic depression, severe depression with psychomotor retardation, "true" treatment-resistant depression, persistent refusal of food, severe suicidality) and for patients with previous positive response to ECT. These patients should be referred to a specialist.

The medication of choice for the maintenance treatment of major depressive disorder (MDD) is either the same dose of the same antidepressant with which remission was achieved in the acute and continuation phase *or* lithium. In the latter case, serum lithium levels (at 12 h after last lithium intake) of 0.5–0.8 mmol/l (mEq/l) are usually recommended and should be monitored regularly. None of the other mood stabilizers used for bipolar affective disorders (e.g., valproate [divalproex], lamotrigine or gabapentin) have been studied for maintenance treatment of MDD in randomized-controlled trials. Although the data from controlled studies is still limited, results verify the efficacy of a variety of antidepressants (TCAs, SSRIs, SNRIs and other "newer" antidepressants) for dysthymic disorder.

1 Unipolar depressive disorders

1.1 Introduction

Unipolar depressive disorders present depressive symptoms only, without any manic symptomatology

or history thereof. This distinguishes them from bipolar affective disorders. Unipolar depressive disorders have been classified into three main diagnostic groups (ICD-10 diagnoses, World Health Organization 1992; corresponding DSM-IV diagnoses (American Psychiatric Association 1994a) are given in parentheses):

- depressive episode or recurrent depressive disorder (DSM-IV: major depressive disorder (MDD) – single episode or recurrent);
- dysthymia (DSM-IV: dysthymic disorder and other chronic depressive disorders (MDD in incomplete remission and chronic MDD)); and
- depressive episode, unspecified, brief recurrent depressions (DSM-IV “subthreshold depressions”).

Of these, major depressive disorder (MDD) has received the most attention in studies. Its treatment – in the acute, continuation and maintenance phases – is therefore the focus of the recommendations developed in these guidelines.

1.2 Goal and target audience of WFSBP guidelines

These WFSBP guidelines provide an update of contemporary knowledge of unipolar depressive disorders and evidence-based recommendations for their treatment. They were developed by the authors and approved by the WFSBP Task Force on Unipolar Depressive Disorders consisting of 46 international researchers and clinicians. The recommendations presented in these guidelines are based on a systematic review of all available evidence pertaining to the treatment of unipolar depressive disorders and embody important clinical and scientific advancements. They also incorporate the opinions of scientifically respected experts and international representatives of the state-of-the-art treatment of these disorders. In the few questions for which a consensus could not be reached, the authors were mandated to make a final judgement.

The guidelines were originally published in 2002 in two parts (Bauer et al. 2002a,b) for use by all physicians, particularly psychiatric specialists. The guidelines presented here have been comprehensively revised and are intended for use by general practitioners encountering patients with depressive conditions, and are thus restricted to the issues most important in the primary care context and to those treatments which are possible within the scope of a general practice. They can serve only as guidelines, because the final judgment regarding any particular treatment procedure must be made by the responsible treating physician in light of the clinical picture

presented by the patient and the diagnostic and treatment options available.

These guidelines deal primarily with biological (somatic) treatment (e.g., antidepressants). Psychotherapeutic treatment interventions are covered only briefly. The guidelines do not address depressive disorders occurring in bipolar affective disorders (which are covered by separate WFSBP guidelines, Grunze et al. 2002, 2003, 2004). Since the availability of medications, treatments and diagnostic procedures varies considerably from country to country, several different treatment options are included in the guidelines.

1.3 Methods of literature search and data extraction

The data used for the development of these guidelines have been extracted from the following sources: Agency for Health Care Policy and Research (AHCPR) Depression Guidelines Panel (1993); AHCPR Evidence Report on Treatment of Depression: Newer Pharmacotherapies (1999); American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Revision (2000); British Association for Psychopharmacology Revised Guidelines for Treating Depressive Disorders (Anderson et al. 2000); Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments, CANMAT, Clinical Guidelines for the Treatment of Depressive Disorders (2000); Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder (Lam and Levitt 1999); Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde, DGPPN, Praxisleitlinien in Psychiatrie und Psychotherapie, Affektive Erkrankungen (2000); The Cochrane Library; World Federation of Societies of Biological Psychiatry WFSBP Guidelines for biological treatment of unipolar depressive disorders (2002); meta-analyses on the efficacy of antidepressant medications identified by a search in the MEDLINE database (up to 1 February 2005); major pertinent review articles identified by a search in the MEDLINE database and textbooks, and individual clinical experience of the authors and members of the WFSBP Task Force on Unipolar Depressive Disorders. All original data quoted were taken from research articles published in peer-reviewed journals in English before 1 February 2005. Important evidence published after this deadline is added and labeled by footnotes.

1.4 Evidence-based classification of recommendations

Each treatment recommendation was evaluated for the strength of evidence for its efficacy, safety and

feasibility.¹ Given the disparities in medication costs across the world, daily treatment costs were not taken into consideration. Four categories of evidence were used:

Level A. Good research-based evidence to support the recommendation. This level is achieved if research-based evidence for efficacy has been derived from at least three moderately large, positive, randomized controlled (double-blind) studies (RCT). At least one of these three studies must moreover be a well-conducted, placebo-controlled study.

Level B. Fair research-based evidence to support the recommendation. This includes evidence of efficacy from at least two moderately large randomized, double-blind studies (this can be either at least two comparator studies *or* one comparator-controlled and one placebo-controlled study) *or* from one moderately large randomized, double-blind study (placebo-controlled or comparator-controlled) and at least one prospective, moderately large (sample size of ≥ 50 participants), open-label, naturalistic study.

Level C. Minimal research-based evidence to support the recommendation. This level is achieved if one randomized, double-blind study with a comparator treatment and one prospective, open-label study/case series (with a sample size of ≥ 10 participants) showed efficacy, *or* at least two prospective, open-label study/case series (with a sample size of ≥ 10 participants) showed efficacy.

Level D. Expert opinion-based (from authors and members of the WFSBP Task Force on Unipolar Depression) supported by at least one prospective, open-label study/case series (sample size ≥ 10 participants).

No level of evidence. Expert opinion for general treatment procedures and principles.

1.5 Epidemiology and course of major depressive disorder

Major depressive disorder (MDD) is a severe mood disorder associated with significant morbidity and mortality affecting individuals of all ages and races. The recent worldwide Global Burden of Disease (GBD) study of the World Health Organization

(WHO) has shown variations by country and region, but patterns and trends for depressive disorders are remarkably similar worldwide (Murray and Lopez 1997a,b). MDD is characterized by single or recurrent major depressive episodes (MDEs). The essential feature of a major depressive episode is a period of at least 2 weeks of depressed mood with abnormalities of neurovegetative function (appetite, weight loss, sleep disturbances), psychomotor activity (e.g., loss of energy and interests, agitation or retardation), cognition (feelings of worthlessness, hopelessness or inappropriate guilt), as well as anxiety and suicidal ideation (Table I). MDD has a median lifetime prevalence of 16.1% (range 4.4–18) (Wittchen 2000; Waraich et al. 2004). It occurs in about 5–10% of the adult population during any 1-year period of time, with women at higher risk than men (the ratio is approximately 2:1) (Regier et al. 1993; Kessler et al. 1994; Picinelli and Gomez-Homen 1997; Ialongo et al. 2004).

At least 10% of all patients presenting in the primary care setting suffer from depression (Üstün and Sartorius 1995; Backenstrass et al. 2006), with about 50% presenting with primarily or only somatic symptoms (Fisch 1987). Of all primary care patients with depressive symptomatology, around 25% classify as having MDD, 30% as having minor depression and 45% present with non-specific depressive symptoms. Seen together, the latter two groups could constitute a subthreshold depression (Backenstrass et al. 2006). Even severely depressed patients are commonly seen in primary care, frequently thinking that because of the severity of their symptoms they might be suffering from a somatic illness.

MDD can begin at any age, even in childhood and adolescence, but there are two peaks in the 20s and 40s (Angst and Preisig 1995; American Psychiatric Association 2000). The mean age of onset of MDD has been estimated around the age of 30 (Wittchen 2000).

Untreated, a typical major depressive episode lasts about 6 months or more (Angst and Preisig 1995; Solomon et al. 1997; American Psychiatric Association 2000; Wang 2004). Modern pharmacotherapy can alleviate suffering during acute episodes, and placebo-controlled trials show that response and remission occur faster in actively treated groups. MDD is a recurrent disorder and 50–85% of the patients who experience an episode will eventually have another (Keller et al. 1986; Mueller et al. 1999).

¹ Note: It is emphasized that a graded efficacy evaluation has its limitations. The strength of a recommendation reflects the scientific evidence on which it is based and not necessarily its importance. Levels of recommendation only apply to treatment and not to other aspects.

Table 1. Classification and criteria of major depressive disorder (DSM-IV) and depressive episode (ICD-10)

ICD-10 ^a (code)	DSM-IV ^b (code)
<p>A. Depressive episode</p> <ul style="list-style-type: none"> • mild (F32.0): at least two typical symptoms, plus at least two other common symptoms; none of symptoms intense • moderate (F32.1): at least two typical symptoms, plus at least three other common symptoms; some symptoms marked • severe (F32.2): all three typical symptoms, plus at least four other common symptoms; some symptoms severe with intensity <p>B. Recurrent depressive disorder (F33): recurrent depressive episodes</p>	<p>Major depressive disorder</p> <p>A. single episode (296.2x) B. recurrent (296.3x)</p>
<p>Abridged criteria of depressive episode: Minimum duration of episode: about 2 weeks</p> <p>Typical symptoms:</p> <ol style="list-style-type: none"> 1. depressed mood 2. loss of interest and enjoyment 3. reduced energy, increased fatigability <p>Other common symptoms:</p> <ol style="list-style-type: none"> 1. reduced concentration and attention 2. reduced self-esteem and self-confidence 3. ideas of guilt and unworthiness 4. agitation or retardation 5. ideas or acts of self-harm or suicide 6. disturbed sleep 7. diminished appetite. 	<p>Abridged criteria major depressive episode:</p> <p>A. Over the last 2 weeks, five of the following features should be present most of the day, or nearly every day (must include 1 or 2):</p> <ol style="list-style-type: none"> 1. depressed mood 2. loss of interest or pleasure in almost all activities 3. significant weight loss or gain (more than 5% change in 1 month) or an increase or decrease in appetite nearly every day 4. insomnia or hypersomnia 5. psychomotor agitation or retardation (observable by others) 6. fatigue or loss of energy 7. feelings of worthlessness or excessive or inappropriate guilt (not merely self reproach about being sick) 8. diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others) 9. recurrent thoughts of death (not just fear of dying), or recurrent suicidal ideation, or a suicide attempt, or a specific plan for committing suicide. <p>B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.</p> <p>C. The symptoms are not due to a physical/organic factor or illness (e.g., a drug abuse, a medication, a general medical condition).</p> <p>D. The symptoms are not better explained by bereavement (although</p> <p>E. this can be complicated by major depression).</p>

^a4th Revision of the American Psychiatric Association's Diagnostic and Statistics Manual (American Psychiatric Association 1994).^b10th Revision of the International Classification of Diseases (World Health Organization 1992).

The prognosis for a depressive episode is good, and most patients return to normal functioning when the episode is over. However, in 20–30% of cases remission is incomplete, with some depressive symptoms persisting chronically (Angst 1986; Keller et al. 1986; Scott 1988; Paykel 1994; Judd et al. 1998; Bauer et al 2002b). MDD is associated with considerable morbidity and mortality, and for many patients an initial episode of depression evolves into a recurrent and debilitating chronic illness with significant and pervasive impairments in psychosocial functioning (Klerman and Weissman 1992; Mintz et al. 1992; Hirschfeld et al. 2000; Judd et al. 2000; Bromberger 2004; Melartin et al. 2004; Papakostas 2004). Studies on the effects of depression on health-related quality of life demonstrate detriments equal to or greater than those for patients with chronic medical illnesses such as

ischemic heart disease or diabetes mellitus (Wells et al. 1989b; AHCP 1999; Unützer et al. 2000a). The symptoms in depressive people with co-morbid medical illnesses tend to show less improvement, and these patients show a higher relapse rate during treatment (Iosifescu et al. 2004).

The most serious consequence of MDD is suicide. A recent meta-analysis showed that while the lifetime prevalence of suicide for the general population is under 0.5%, that of patients with affective disorders ranges from 2.2% for mixed inpatient/outpatient populations to 8.6% for those who have been hospitalized for suicidality (Bostwick and Pankratz 2000). Depression also substantially increases the risk of death by cardiovascular disease (Wulsin et al. 1999).

The Global Burden of Disease Study estimated that unipolar major depression is the fourth largest

contributor to the global burden of disease (premature mortality and disability). With the addition of suicide, the burden of unipolar major depression increased by nearly 40% (Murray and Lopez 1997a). By the year 2020, unipolar MDD is projected to be the second largest contributor to the global burden of disease after heart disease (Murray and Lopez 1997b).

In addition to the personal suffering of individuals and their families, depression imposes significant costs on society (Brunello et al. 1995; Thase 2001; Fava et al. 2003a; Greenberg et al. 2003; McIntyre and O'Donovan 2004), even more so when not properly diagnosed or undertreated (Wells et al. 1989a; Üstün and Sartorius 1995; Unützer et al. 2000b, Young et al. 2001).

1.6 Indications and goals of treatment for major depressive disorder

Antidepressant treatment should be considered for patients who meet diagnostic criteria for depressive episode (ICD-10) or major depressive disorder (DSM-IV) (see Table I). Guidelines differ with respect to the recommendation of antidepressants in mild depressive episodes or depression in primary care (Depression: management of depression in primary and secondary care – NICE Guideline 2004; Practice guideline for the treatment of patients with major depressive disorder, APA 2000). Depending on individual characteristics and/or requests of the patient antidepressant treatment might be indicated, otherwise psycho- and sociotherapeutic approaches alone may be sufficient.

Current diagnostic criteria in both classification systems represent a clinical and historical consensus on the most prominent and important symptoms and signs of depressive illness (Table I).

Before initiating treatment, the general practitioner should take the patient's preferences and previous treatment experiences into consideration. Especially if a patient exhibits psychotic features (e.g., delusions) or suicidality or if the depression occurs in the context of a bipolar illness, treatment by a specialist or inpatient treatment is indicated. See Figure 1 for a stepped-care model. Early recognition of bipolar disorder is especially important since treatment approaches differ substantially from those for unipolar depression and early appropriate treatment positively influences long-term outcome. Bipolar patients are over-represented in treatment-resistant patients falsely diagnosed with unipolar depressive disorder and antidepressant treatment alone seems to have unstabilizing impact on the course of the disease (Ghaemi 2002). Apart from asking the patient and his family about manic or hypomanic symptoms, screening instruments could help to identify those patients (e.g., Mood Disorders Questionnaire, MDQ, Hirschfeld 2000; Hypomanic Checklist, Angst et al. 2003, 2005).

The treatment of major depressive disorder requires conceptualization of acute, intermediate and long-term goals. Kupfer and colleagues (Kupfer 1993) have developed a model for the typical course of a major depressive episode including the risk of recurrence and corresponding structured treatment approach. In this model, the three phases of treatment correspond to three stages of the illness: (1) acute therapy, (2) continuation therapy, and (3) maintenance therapy (see Figure 2).

The *acute phase* of therapy is the time period from the initiation of treatment to remission, which is the primary therapeutic goal (Frank et al. 1991; Kupfer 1993). The *continuation phase* follows the acute phase to preserve and stabilize the remission. It is

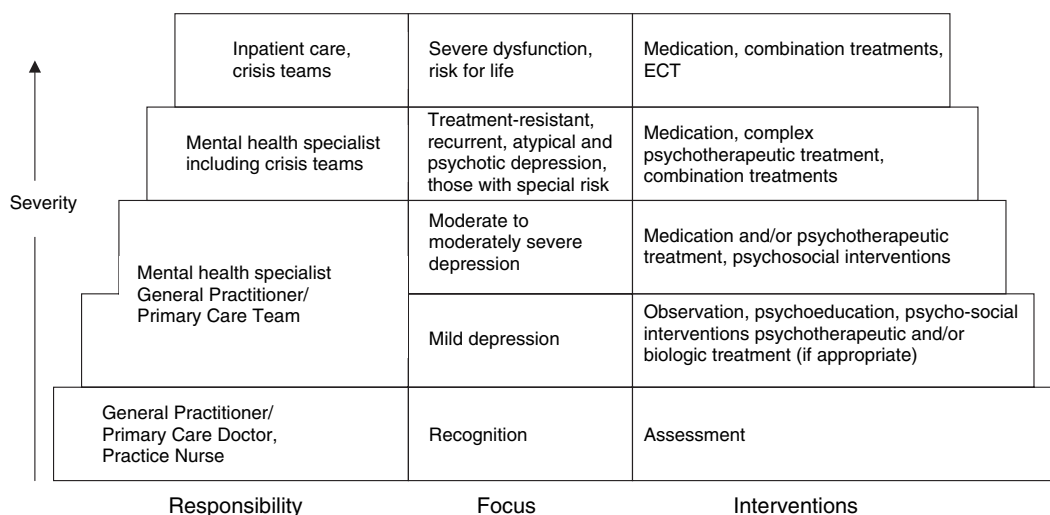


Figure 1. Stepped-care model (adapted version, original idea from NICE guideline (2004)).

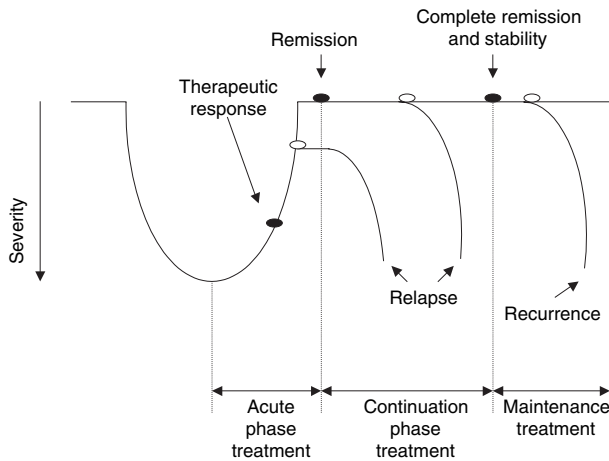


Figure 2. Phases of disease and treatment (adapted version, original from Kupfer (1991)).

the phase in which the treatment is extended for a period of time in order to prevent a return of the depression. If the depressive syndrome returns during the continuation therapy, a relapse has occurred. When the patient has been asymptomatic for approximately 6 months, a recovery from the episode has occurred. The recovery may be confirmed by continued absence of depressive symptoms after the cessation of medication. Recovery applies only to individual episodes of the illness and does not imply the patient would be free of recurrences (Bauer and Helmchen 2000; Möller et al. 2003). Maintenance (prophylactic) treatment is aimed at preventing a new episode of depression and suicide.

2 Acute-phase treatment of major depressive disorder

These guidelines become applicable at the point when (1) the diagnosis of a major depressive episode has been made by a physician according to one of the two established classification systems, the International Classification of Diseases (ICD-10, World Health Organization 1992) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association 1994a (Table I) and when the practitioner has thoroughly considered: (2) any concurrent psychiatric disorders (mania, schizoaffective disorders, alcohol or substance abuse/dependence, anxiety disorders, eating disorders, personality disorders) and somatic disorders (e.g., endocrine, neurological, autoimmune, infectious disorders, carcinomas), as well as (3) any other factors (e.g., non-psychiatric medications or psychosocial stress factors) that might contribute to a depressive syndrome or interfere with treatment. It is the task of the physician to make the initial

assessment of depression, encompassing a thorough somatic examination.

The most common treatments for major depressive disorder will be reviewed below, with a focus on somatic treatment interventions. Components of psychiatric management and general “psychotherapeutic support” (American Psychiatric Association 2000) should be initiated and continued throughout the entire treatment. These components include: determining the treatment plan and treatment setting; establishing and maintaining a therapeutic alliance; monitoring and reassessing psychiatric status (including the patient’s risk for suicide); reassessing the adequacy of diagnosis; monitoring the patient’s treatment response, side effects and general medical condition, and enhancing treatment adherence by providing education to patients and families (American Psychiatric Association 2000). During the acute treatment phase, weekly or bi-weekly visits are recommended where feasible. During the continuation phase, the frequency of visits may vary, but a frequency of one visit every 1–2 months is recommended.

2.1 Antidepressants

The development of antidepressant medications is one of the most important achievements in the treatment of major depression. Many different types have been introduced to the pharmacotherapeutic armamentarium. At least 38 different antidepressants are available worldwide, but market availability varies considerably from country to country (Table II).

The “newer” antidepressants were developed with a view to reduced side effects, the classes of antidepressants currently available differ little in their antidepressant efficacy, all producing treatment responses of 50–75%.

The selection of a particular antidepressant for the individual patient therefore depends on various factors (adapted from AHCPR 1993): patient’s prior experience with medication (positive/negative response), concurrent medical conditions that may be worsened by selected antidepressants (e.g., metabolic syndrome), concomitant use of nonpsychiatric medications that may lead to negative drug–drug interactions (see Table IV), a drug’s short- and long-term side effects (those side effects which affect quality of life are critical for patients’ satisfaction and compliance), physician’s experience with the medication, patients’ history of adherence to medication, history of first-degree relatives responding to a medication, patient preferences, and the cost and availability of specific antidepressants.

Table II. Antidepressants: Mode of action and commonly used doses.

Generic Name ^a (in alphabetical order)	Traditional structural classification ^b	Classification according to neurochemical action ^b	Starting dose ^c (mg/day)	Standard dose ^d (mg/day)	Plasma levels ^e (therapeutic range) (ng/ml)
Agomelatine		MT agonist	25	25–50	
Amineptine			100	200–300	
Amitriptyline ^f	TCA		25–50	100–300	80–200*
Amoxapine	TetraCA		50	100–400	
Bupropion ^g		NDRI	150	150–450	
Citalopram ⁱ		SSRI	20	20–40 (60)	
Clomipramine ^{h,i}	TCA		25–50	100–250	175–450*
Desipramine	TCA		25–50	100–300	100–300
Dibenzepine	TCA		120–180	240–720	
Doslepine	TCA		75	75–150	
Dothiepin	TCA		25–50	100–300	
Doxepine ⁱ	TCA		25–50	100–300	
Duloxetine ^k		SNRI	30–60	60–120	
Escitalopram ⁱ		SSRI	10	10–20	
Fluoxetine ^h		SSRI	20	20–60	
Fluvoxamine ^h		SSRI	50	100–200	
Imipramine	TCA		25–50	100–300	175–300*
Isocarboxazid ⁱ			20	20–60	
Lofepramine	TCA		70	140–210	
Maprotiline	TetraCA		25–50	150–225	
Mianserin	TetraCA	§	30	60–120	
Milnacipran		SNRI	50–100	100–200	
Mirtazapine		Other\$	15	15–45	
Moclobemide		RIMA	150	300–600	
Nefazodone			100	300–600	
Nortriptyline	TCA		25–50	75–200	70–170
Paroxetine ^{h,i,j}		SSRI	20	20–40 (60)	
Phenelzine ⁱ		MAOI	15	30–90	
Protriptyline	TCA		10	20–60	
Reboxetine		NARI	4–8	8–12	
Sertraline ^{h,i,j}		SSRI	50	50–150	
Setiptiline	TetraCA		3	3–6	
Tianeptine		Other#	37.5	37.5	
Tranlycypromine ⁱ		MAOI	10	20–60	
Trazodone			50–100	200–600	
Trimipramine ^{f,i}	TCA		25–50	100–300	
Venlafaxine ^j		SNRI	37.5–75	75–375	195–400*
Viloxazine			100	200–500	

^aAvailability on the market differs considerably across countries.

^bAbbreviations see below.

^cLower starting doses may be needed for older adults (>60) or patients with co-morbid medical illness (especially cardiovascular conditions; see text).

^dStandard doses are generally lower in Japan.

^eOnly given for those antidepressants with well established therapeutic range (Perry et al. 1994).

*Recommended therapeutic range is the sum of the drug and the active metabolite

Other indications than depression (approved in some countries) or common uses: ^fchronic pain; ^gsmoking cessation; ^hobsessive-compulsive disorder (OCD); ⁱanxiety disorders (panic disorders, PTSD, social phobia); ^jgeneralized anxiety disorder; ^kdiabetic and peripheral neuropathic pain, stress urinary incontinence.

Abbreviations: MAO-I, irreversible inhibition of monoamine oxidase (MAO); MT agonist, agonist of the melatonin receptor (MT1 and MT2); NARI, noradrenaline reuptake inhibition; NDRI, noradrenaline and dopamine reuptake inhibition; Other, other types of receptor or transmitter profile; RIMA, reversible inhibition of monoamine oxidase A (MAO-A); SNRI, selective serotonin and noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant. TetraCA, tetracyclic antidepressant.

§Noradrenaline reuptake inhibition plus presynaptic α 2-blockade; \$ α 2-antagonist; #5-HT reuptake enhancer.

2.1.1 Classification and efficacy. Unfortunately, the classification of antidepressants used in clinical practice does not always reflect a systematic approach. Traditionally, antidepressant medications have been grouped into the following main cate-

gories: tricyclic antidepressants (TCA), tetracyclic antidepressants (both are non-selective serotonin and norepinephrine reuptake inhibitors), selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (NRIs), selective

serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOI) (including irreversible MAOIs and reversible inhibitors of monoamine oxidase A [RIMA]), and “other” antidepressants.²

The “older” antidepressants have, in numerous placebo-controlled studies, proved effective in treating major depressive disorder. They include the tricyclics, tetracyclics and irreversible MAO inhibitors (all classes Level A) (Khan et al. 2000; Storosum et al. 2001; Fiedorowicz and Swartz 2004). Similarly, numerous double-blind controlled trials have demonstrated superior efficacy of the SSRIs compared to placebo (Level A) (AHCPR 1999; Bech et al. 2000; Khan et al. 2000; Mace and Taylor 2000). In addition, the efficacy of SNRIs compared to placebo has been demonstrated in numerous double-blind controlled trials (Level A) (Entsuah et al. 2001; Hirschfeld and Vornik 2004). For mirtazapine the efficacy compared to placebo is also well documented (Level A) (Bech 2001). Recently agomelatine, a melatonergic antidepressant, has also shown antidepressant efficacy in clinical trials versus placebo (Kennedy and Emsley 2006*).

The “older” (irreversible) MAO inhibitors (e.g., tranlycypromine and phenelzine) are not considered first-line treatments. Although their efficacy is comparable to tricyclic antidepressants, they entail the risk of potentially fatal hypertensive crisis or serotonin syndrome (see below) in patients who eat foods containing tyramine (e.g., aged cheese, aged or cured meats, soy sauce and soy bean condiments, salted fish, and red wine; see manufacturer’s warning notices) or use certain medications (Level B) (American Psychiatric Association 2000).

2.1.2 Comparative efficacy and tolerability. The numerous tricyclics do not differ among themselves in terms of efficacy, but do show different side effect profiles (Level A) (Table III) (Hotopf et al. 1997). With respect to SSRIs, a meta-analysis has shown no significant difference in efficacy between the individual compounds (Level A) (Edwards and Anderson 1999).

In general, there are no clinically significant differences in efficacy and effectiveness between tricyclic antidepressants and SSRIs (Level A) (Möller et al. 1994; American Psychiatric Association 2000; Anderson 2000; Bech et al. 2000; Geddes et al. 2001). One meta-analysis of 102 RCTs did show evidence that TCAs may be slightly more

effective than SSRIs in hospitalized patients and severely ill patients (Level A) (American Psychiatric Association 2000; Anderson 2000; see also Danish University Antidepressant Group 1986 Group 1990). However, another meta-analysis of fewer RCTs using a different methodology found that the advantage of TCAs over SSRIs did not reach statistical significance (Geddes et al. 2001).

SSRIs are generally tolerated better than TCAs and show lower rates of treatment discontinuation (Level A) (Simon et al. 1996; AHCPR 1999; Anderson 2000; Bech et al. 2000; Peretti et al. 2000; see also the review by Vaswani et al. 2003). SSRIs are safer and have higher tolerability profiles than tricyclic and tetracyclic antidepressants, causing fewer anticholinergic side effects and cardiovascular toxicities (Level A) (Mace and Taylor 2000; Peretti et al. 2000; Ray et al. 2004). SSRIs and other “newer antidepressants” are therefore first-choice medications for mild (when appropriate) to moderate depression, particularly in the outpatient and primary care setting, and in patients with cardiovascular diseases (Kasper 1997; Shores et al. 1998; Sauer et al. 2001; Alvarez and Pickworth 2003).

Regarding the “newer” antidepressants, recent meta-analyses have suggested that the SNRI venlafaxine is more effective than SSRIs (Einarson et al. 1999; Anderson 2001; Thase et al. 2001; Stahl et al. 2002) and other antidepressants (Smith et al. 2002).

For severe depression, TCAs, SSRIs and SNRIs can be recommended, as well as ECT, if appropriate (see 2.3) (Level B).

The NRI reboxetine is not different in efficacy from the SSRI fluoxetine but accompanied by less study drop-outs (meta-analysis, Cipriani et al. 2005*). Compared to another SSRI (citalopram) reboxetine showed comparable efficacy and less resulting sexual dysfunction (the drop-out rate was higher for reboxetine, possibly due to missing dose titration in the beginning, Langworth et al. 2006*).

Side effects vary between classes of antidepressants and to some extent between individual agents (Table III). An agent may have a side effects profile which makes it particularly suitable for patients with specific concurrent nonpsychiatric medical conditions. For patients with coronary artery disease, for example, drugs that do not lower blood pressure or are not associated with changes in cardiac conduction (e.g., bupropion, SSRIs, mianserin) are preferable. Among the tricyclics, the secondary amines (e.g., desipramine, nortriptyline) have fewer side

² Note: Abbreviations used for antidepressant groups vary in the literature. For example, selective norepinephrine reuptake inhibitors are abbreviated as NRI or SNRI, selective serotonin and norepinephrine reuptake inhibitors as SSNRI or SSNRI.

* Published after the date of systematic literature search

Table III. Side effect profiles of antidepressants.^a

Generic name (in alphabetical order)	Anticholinergic ^b	Nausea /gastrointestinal	Sedation	Insomnia /agitation	Sexual dysfunction	Orthostatic hypotension	Weight Gain	Specific adverse effects	Lethality in overdose
Agomelatine	-	+	-	-	-	-	-		Low
Amineptine	-	+	-	+	+	+	+		Low
Amitriptyline	+++	-	++	-	+	++	++	Risk of abuse (amphetamine-like effects)	High
Amoxapine	+++	-	+	+	+	+	+	ECG changes ^c ; may lower seizure threshold hyperprolactinemia	High
Bupropion	+	+	-	+	-	-	-		Low
Citalopram	-	+	-	+	+	+	+		Low
Clomipramine	+++	+	+	+	+	+	+	ECG changes ^c ; may lower seizure threshold	Moderate
Desipramine	+	-	-	+	+	+	+		High
Dibenzepine	+	-	+	-	+	+	+		Moderate
Doslepine	+	-	++	-	+	+	+		High
Dothiepin	+++	-	+++	-	+	+++	+++		High
Doxepine	+++	-	+++	-	+	+++	+++		High
Duloxetine	-	+	-	+	+	-	-		Low
Escitalopram	-	+	-	+	+	-	-		Low
Fluoxetine	-	+	-	+	+	-	-		Low
Fluvoxamine	+	+++	+	+	+	+	+		Low
Imipramine	++	-	+	+	+	++	++	ECG changes ^c ; may lower seizure threshold	High
Isocarboxazid	+	+	-	+	+	++	++	Hypertensive crisis ^c ; risk of serotonin syndrome ^f	High
Lofepramine	+	-	+	+	+	+	+	ECG changes ^c ; may lower seizure threshold	Low
Maprotiline	++	-	++	-	+	++	++	Increased seizure risk	High
Mianserin	+	-	++	-	-	+	+	Blood dyscrasia (rare)	Low
Milnacipran	-	++	++	+	+	-	-		Low
Mirtazapine	-	-	++	-	-	+	+		Low
Moclobemide	+	+	-	+	-	-	-		Low
Nefazodone	+	+	++	-	-	+	+	Inhibitory effects on CYP3A4 ^d	Low
Nortriptyline	+	-	++	+	+	+	+	ECG changes ^c ; may lower seizure threshold	High
Paroxetine	+	++	-	++	++	-	+	Inhibitory effects on CYP2D6 ^d	Low
Phenelzine	+	+	+	++	++	++	++	Hypertensive crisis ^c ; risk of serotonin syndrome ^f	High
Protriptyline	+++	-	+	++	++	++	++	ECG changes ^c ; may lower seizure threshold	High
Reboxetine	+	+	-	++	++	++	++		Low
Sertraline	-	+	-	++	++	-	-		Low
Setipiline	+	+	++	-	+	+	+		Moderate
Tianeptine	+	-	++	-	+	-	-	ECG changes ^c ; may lower seizure threshold	Low
Tranlycypromine	-	+	-	+	-	+	-	Hypertensive crisis ^c ; risk of serotonin syndrome ^f	High
Trazodone	-	+	++	-	++	+	+	Priapism (rare)	Low
Trimipramine	++	-	+++	-	++	++	++	ECG changes ^c ; may lower seizure threshold	High
Venlafaxine	-	+	-	++	++	-	-	Hypertension	Low
Viloxazine	-	+	-	++	+	-	-		Low

Categories of side effect strength: + + + +, high/strong; + + +, moderate; +, low/mild; -, very low/none.

^aThese side effect profiles of antidepressants are not comprehensive and are for rough comparison only. Details of drugs used and potential cautions and interactions should be looked up in textbooks/reviews (e.g., Bezchlibnyk-Butler and Jeffries 1996, Benkert and Hippus 2005; Kent 2000), the primary literature or the complete prescribing information available in the package insert of the drug.

^bThese refer to symptoms commonly caused by muscarinic receptor blockade including dry mouth, sweating, blurred vision, constipation and urinary retention.

^cConduct delays.

^dOnly those inhibitory effects on hepatic CYP450 enzymes are shown that are clinically relevant; for details see Brösen (1998) and Kent (2000).

^eIncreased risk with high tyramine containing food and sympathomimetic drugs.

^fIn combination with serotonergic drugs.

effects than do the tertiary amines (e.g., amitriptyline, imipramine).

The most frequent side effects of TCAs and tetracyclics are: anticholinergic/antimuscarinergic (dry mouth, constipation, blurred vision, urinary hesitation, and tachycardia), cardiovascular (α -adrenergic blockade, orthostatic hypotension, bradyarrhythmias, tachycardia), antihistaminergic (sedation, weight gain), and neurological (mild myoclonus, seizures in overdoses, delirium in elderly patients) (Table III). TCAs and tetracyclics should therefore not be used in patients with moderate to severe cardiovascular disorders (Shores et al. 1998), narrow-angle glaucoma, prostatic hypertrophy, cognitive impairment, seizures or delirium.

The most frequent side effects of SSRIs are: gastrointestinal (nausea, vomiting and diarrhea), activation/restlessness (exacerbation of restlessness, agitation, sleep disturbances), sexual dysfunction (loss of erectile or ejaculatory function in men, loss of libido and anorgasmia in both genders) and neurologic (exacerbation of migraine headaches and tension headaches) (Table III). The use of SSRIs is contraindicated in combination or shortly before/after treatment with MAO inhibitors because of the risk of serotonin syndrome. The most frequent clinical features of the serotonin syndrome are changes in mental status, restlessness, myoclonus, hyperreflexia, shivering, abdominal pain, diarrhoea and tremor (Sternbach 1995; Finfgeld 2004). The serotonin syndrome is most commonly the result of the interaction between irreversible MAO inhibitors and SSRIs but can also occur with other serotonergic agents (e.g., clomipramine, l-tryptophan, fenfluramine, buspirone, venlafaxine, milnacipran, nefazodone, and trazodone).

Side effects with SNRI (venlafaxine, milnacipran and duloxetine) resemble those of SSRIs. Blood pressure should be monitored for possible elevation. With mirtazapine weight gain may be induced.

Antidepressants differ with regard to the sexual side effects which incur from their usage (Ferguson 2001; Montejo et al. 2001; Montgomery et al. 2002; Damsa et al. 2004). TCAs, SSRIs and venlafaxine more likely result in sexual dysfunction than duloxetine and reboxetine (Werneke et al. 2006*). For managing antidepressant sexual side effects, see Zajecka (2001) and Worthington and Peters (2003).

The degree of benefit attained from adequate treatment appears to increase proportionally with the severity of depression (Angst and Stassen 1994). For mild depressive episodes, the benefit of treatment with antidepressants is uncertain; education, support and problem solving are treatment alter-

natives (Level B) (Anderson et al. 2000; Depression: management of depression in primary and secondary care – NICE Guideline 2004).

2.1.3 Suicidality. Suicide is a major risk in patients with major depression. It should be assessed from the start and reviewed regularly over the course of treatment. Factors alerting the general practitioner to a patient at high risk of suicide are: affective illness, poor impulse control, age and gender (males between age 20 and 30 and over age 50 years and especially very old males; and females between age 40 and 60), history of previous suicide attempt (being the most relevant factor), family history of suicidal behaviour, positive family history of early-onset affective disorder, substance abuse (particularly alcohol abuse), marital status (single, divorced or widowed), sudden change in socioeconomic status (loss of job, financial problems, undesired retirement), and lack of support (Blumenthal 1990; Appleby 1992; Nordstrom et al. 1995a,b; Angst 1999b; Bostwick and Pankratz 2000; Möller 2003). If the patient has suicidal thoughts or intent, close surveillance and specialist treatment are necessary and admission to a psychiatric ward is recommended (Figure 1). Hospital admittance without patient consent may be necessary. Immediate and intensive care should be initiated and should include intensive pharmacotherapy and psychotherapy addressing psychosocial factors. There is no specific, acutely acting “anti-suicidal” medication.

Many clinicians have successfully added antipsychotics or benzodiazepines (Furukawa et al. 2001) to the treatment regimen. (For information on treatment recommendations for MDD with psychotic features [delusional depression], see 2.6.1 [Antipsychotics]). For patients considered likely to take an overdose, it is recommended to prescribe only one week’s supply of potentially lethal antidepressants (e.g., the TCAs or irreversible MAO inhibitors) at a time, and the antidepressant chosen should be one which is relatively safe if it is indeed taken in overdose (Table III; AHCPR 1993).

Epidemiological studies revealed a reduction of the frequency of suicides and increased prescriptions of antidepressants within the last decades. In contrast, there is a debate on whether certain antidepressants, or antidepressants in general, potentially increase the risk of suicidal behaviour. Clinical conditions as co-morbid personality disorders and inadequate treatment of bipolar depression may be of importance within this context.

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Some data suggest that treatment with SSRIs, potentially with other antidepressant drug classes too, the risk of suicidality (preferentially suicidal attempts) maybe increased in some patients (Möller 2006*). This risk might be pronounced in the initial phase of treatment (Jick et al. 2004). Simon and colleagues showed that the risk of suicide is highest in the month before starting an antidepressant, much lower in the first week of treatment, thereafter dropping to even lower, stable rates (data from computerized health plan records of 65,000 patients with depression, Simon et al. 2006*). Khan et al. compared the incidence of suicide and suicide attempts with several of the “newer” antidepressants and placebo and did not find statistically significant differences (Khan et al. 2000).

However, the concerns mentioned above have induced official warnings (e.g., by the US Food and Drug Administration 2005), especially for child and adolescent psychiatry as here for most antidepressants efficacy has not been demonstrated. In medical decision making, the potential risk should be carefully balanced with the benefit of antidepressive treatment. Consideration of the individual disease history including risk factors for suicidal behaviour and close observation of the patient (e.g., every week in the first weeks of treatment) are recommended when starting antidepressant treatment.

2.1.4 Evaluating the efficacy of the initial treatment. The general practitioner can evaluate the efficacy of the initial treatment by defining a time period in that context and then performing a reasonable assessment of the patient’s response to the antidepressant. This may include (apart from clinical global impression) the use of patient self-rating scales (e.g., Beck Depression Inventory [BDI, Beck 1961], or the nine-item module of the Patient Health Questionnaire [PHQ-9; Spitzer et al. 1999]) and/or observer-ratings scales (e.g., Hamilton Rating Scale for Depression [HRSD; Hamilton 1960] or the Montgomery–Asberg Depression Rating Scale [MADRS; Montgomery and Asberg 1979] (Rush and Kupfer 2001).

Criteria recommended for clarifying the relevant terms of treatment response are:

- nonresponse: $\leq 25\%$ decrease in symptom severity compared to baseline
- partial response: 26–49% decrease in symptom severity compared to baseline
- response: $\geq 50\%$ decrease in symptom severity compared to baseline

- response with residual symptoms: response with partial remission
- remission: absence of symptoms defined by absolute scale score (sometimes called full response or full remission, for example a HRSD score of ≤ 7).

After a period of about 2–4 weeks of antidepressant treatment response should be evaluated and if insufficient, optimization strategies should be implemented. At least 8–10 weeks maybe required to define the full extent of symptom reduction (Rush and Kupfer 2001). If the initial treatment must be discontinued due to intolerable side effects, a switch to a different treatment is called for (for additional treatment options see below).

2.1.5 When to declare initial treatment failure. When to discontinue treatment with an antidepressant should be decided by the physician and the patient in collaboration, since the right moment for a change in the treatment plan is crucial. Changing the treatment strategy too early may lead to false conclusions, e.g., that the medication is ineffective, and discourage the patient. In contrast, persisting over a too long period without any response may lead to unnecessary prolongation of the patients’ suffering and duration of the episode.

The general consensus is that if the patient does not show any improvement after 2–4 weeks of treatment with an antidepressant dose at the upper level of the standard dose (Table II), it becomes less likely that he/she will respond to this particular medication later. If the patient is showing a partial response after 2–4 weeks it becomes more likely that the patient will respond after 8–12 weeks of therapy (Stassen et al. 1996; Szegedi et al. 2003). There is some evidence that older adults may take longer to show a response to “older” antidepressant medications (up to 12 weeks, Katona 1994). However, recent studies with SSRI suggest, that here older patients may not routinely require longer time to show response (see Sackeim et al. 2005).

2.1.6 Diagnostic reassessment and optimizing antidepressant medication. Before considering a switch in the treatment strategy, the first step should be a reappraisal of the diagnosis and adherence to the current treatment regimen. It may be important to take pharmacokinetic factors that affect plasma levels of antidepressants into consideration. If available, plasma levels of tricyclic antidepressants can be helpful in evaluating the adequacy of the dosage and the need for dose

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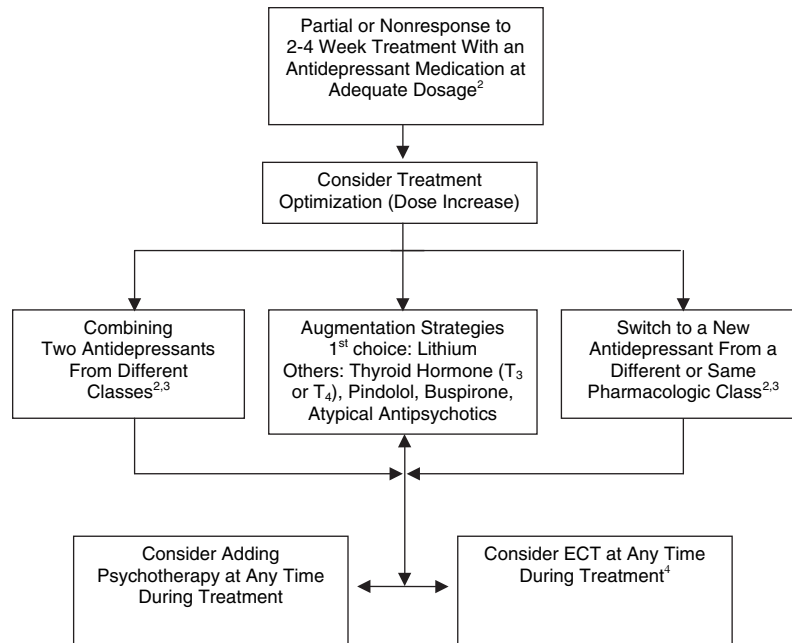


Figure 3. Flow Chart: Therapeutic options in partial and nonresponders¹ to initial treatment with an antidepressant in major depressive disorder. ¹Partial response: 26–49% decrease in baseline symptom severity; nonresponse: $\leq 25\%$ decrease in baseline symptom severity. ²See Table II. ³Caution with combining irreversible MAO inhibitors (see 2.1.8.2). ⁴For indications see 2.3.

adjustment (see below and Table II). A review of the findings from physical examinations and laboratory results is wise to avoid overlooking coexisting general medical conditions, poorly controlled pain, non-psychiatric medications or hidden substance abuse that may underlie or be associated with the depressive episode. Persistent psychosocial stressors are also considered as a reason for non-response to treatment. Reevaluation of the adequacy of the medication dose is also advised. Often an optimization of the treatment can be achieved by increasing the dose of the antidepressant (Figure 3). This strategy is particularly useful for patients receiving TCAs, but there is less evidence to support it in SSRI-treated patients (Baker et al. 2003). Licht and Qvitzau even found a lower response rate with a substantial dose increase of sertraline than with staying at the same (moderate) dose for another 5 weeks (Licht and Qvitzau 2002). For a review see Adli et al. (2005*).

2.1.7 Therapeutic drug monitoring. Therapeutic drug monitoring (TDM) involves measuring the plasma concentration of a drug to ascertain whether concentrations are above, below or within an optimal therapeutic range. Other indications for TDM are to determine absorption and compliance with medication ingestion. Unlike with some tricyclic antidepressants, there is no clear relationship between

clinical efficacy and plasma concentration of SSRIs, nor any threshold that defines toxic concentrations; therefore, routine monitoring of SSRI plasma levels cannot be recommended (see also Adli et al. 2005*). Plasma concentrations of antidepressants vary considerably among patients treated with similar dosages (Hiemke and Härtter 2000; Kent 2000).

2.1.8 Treatment options for the partial and non-responding patient. Regardless of the initial choice of antidepressant, at least 30% of depressions will not respond sufficiently to treatment (Thase and Rush 1995; Tranter et al. 2002; Nelson 2003). Various alternative treatment strategies have been proposed for these non- or partially responsive depressions (Amsterdam 1991; Nolen et al. 1994; Marangell 2001; Shelton 2003; Pridmore and Turnier-Shea 2004). The major types of strategies employed after reviewing correctness of diagnosis and sufficiency of drug dosing and compliance, are (1) switching to another antidepressant from a different pharmacological class (e.g., from a SSRI to a TCA), (2) switching to another antidepressant within the same pharmacological class (e.g., from a SSRI to another SSRI), (3) combining two antidepressants from different classes (e.g., a TCA plus a SSRI), (4) augmenting the antidepressant with other agents (e.g., lithium or thyroid hormone) to enhance antidepressant efficacy, and (5) combining the antidepressant with

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a psychotherapeutic intervention. These strategies have been examined in a variety of agents and combinations; however, most studies have not been subjected to rigorous scientific investigation or have included small study groups.

Currently, no clear consensus exists on which strategy should be favoured for the non-responding patient, since to date no rigorous trial with a randomized, double-blind design has been conducted to answer this question (Crismon et al. 1999; Lam et al. 2004). Finally, some authors have argued in favour of augmentation strategies, e.g., lithium, because they have been repeatedly investigated in placebo-controlled trials.

2.1.8.1 Strategy 1: Switching to another antidepressant from a different class. The advantage of a switch to another antidepressant class is that it minimizes polypharmacy, which helps prevent toxicity and negative drug–drug interactions, it may lead to fewer or more tolerable side effects and can, therefore, improve patient compliance (Reynaert-Dupuis et al. 2002; Thase et al. 2002; Fava et al. 2003b).

Switching from an SSRI to, e.g., novel dual-acting antidepressants, selective norepinephrine or norenergic/dopaminergic agents, tricyclic antidepressants or mianserin appears legitimate (see Ruhe et al. 2006* for a systematic review).

Disadvantages in such a switch are the loss of partial efficacy by switching from initial antidepressant and the relatively long period until the second agent can develop its antidepressive activity (delayed onset compared to augmentation or combination).

With longer use of most antidepressants step-down discontinuation within a period of 1–2 weeks is recommended rather than abrupt discontinuation, for this may cause withdrawal symptoms. Switching from or to an irreversible MAO inhibitor should be performed with caution and with a 2-week wash-out period between the two drugs (5 weeks with switch from fluoxetine) (Level B).

2.1.8.2 Strategy 2: Switching to another antidepressant from the same class. This has especially been demonstrated in a series of open-label studies showing that patients not responsive to one SSRI have a 40–70% chance of responding to a second SSRI (Level C) (Thase and Rush 1997). Another study has shown response rates from 50 to 60% when switching to another SSRI (Howland and Thase 1999).

2.1.8.3 Strategy 3: Combining two antidepressants from different classes. Reasons in support of such combination treatment include avoidance of loss of

partial response with a monotherapy and less fear of worsening of depressive symptoms when a partially effective medication is discontinued. Disadvantages of this strategy are the increased risk of drug–drug interactions, potentiation of side effects and drug costs. Although often applied in clinical practice, few controlled data in support of the utility and efficacy of this strategy exist (Level C, applies to all combinations, Licht and Qvitzau 2002; De Battista et al. 2003). Combining irreversible MAO inhibitors with SSRIs and other antidepressants which act on the serotonergic system (e.g., clomipramine, venlafaxine) must be strictly avoided due to potentially fatal interactions (serotonin syndrome). Similarly, combinations of an SSRI with l-tryptophan must be avoided. See systematic review on combination by Dodd et al. (2005*).

In the STAR*D trial, the second-generation antidepressant bupropion or the anxiolytic buspirone added to the SSRI citalopram in patients that did not respond sufficiently to citalopram alone resulted in remission rates of about 30% in each group (Trivedi et al. 2006; for design issues of this multi-site, prospective, sequentially randomized trial in psychiatric depressed outpatients, see Rush et al. 2004).

2.1.8.4 Strategy 4: Augmentation of antidepressants. This type of augmentation therapy involves adding a second drug other than an antidepressant to the treatment regimen when no response or only partial response has been achieved, with the goal of enhancing treatment. One advantage of augmentation is that it eliminates the period of transition between one antidepressant to another and builds on the partial response. Consequently, when they work, augmentation strategies can have a rapid effect. Secondly, augmentation is of benefit for patients who have had some response and may be reluctant to risk losing that improvement.

Numerous augmentation strategies have been described for use in treatment-resistant depression. Of these, lithium is the most important and best-documented, with more than 27 open studies and 10 placebo-controlled trials in the acute treatment phase of unipolar and bipolar depression (Level A, Review: Fawcett 2003; Bauer et al. 2006*). Adding lithium to ongoing antidepressant treatment is thus recommended as the first choice of an augmentation strategy (Bauer and Döpfner 1999). Lithium has been found to augment the therapeutic effects of a broad spectrum of antidepressants including TCAs (Joffe et al. 1993; Katona et al. 1995) and SSRIs (Katona et al. 1995; Baumann et al. 1996; Zullino and Baumann 2001). A meta-analysis including 10

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prospective studies provided firm evidence that lithium augmentation is superior to placebo in unipolar major depression, with response rates on average of 41.2% in the lithium group and 14.4% in the placebo group (Crossley and Bauer, in press). Lithium augmentation should be administered for 2–4 weeks in order to allow assessment of the patient's response. The recommended lithium doses (about 20–30 mmol/day) characteristically achieve serum lithium levels of 0.6–0.8 mmol/l (Bschor et al. 2003). In the case of response, lithium augmentation should be continued for at least 12 months (Bauer et al. 2000; Bschor et al. 2002).

Studies assessing the effects of thyroid hormones in treatment-resistant depression have largely focused on T₃ as the augmenting thyroid hormone. Numerous case series and at least 13 prospective trials (nine open and four controlled double-blind studies) have evaluated the use of T₃; most studies administered 25–37.5 µg/day T₃ to potentiate the response to TCAs in non-responders (Level B) (Joffe et al. 1993; Altshuler et al. 2001). However, not all controlled double-blind studies yielded significant results in favour of T₃. A subsequent meta-analysis did not find consistent results in favour of T₃ augmentation (Aronson et al. 1996). A small number of open studies have reported response rates of about 50% for treatment-resistant depressed patients using higher, supraphysiological doses of l-thyroxine (T₄) (Level D) (Bauer et al. 1998, 2005). Thyroid hormones should be administered with caution because of potential unwanted effects.

Another more recent strategy is to combine antidepressants with an atypical antipsychotic. Mainly open studies and case series show favourable outcomes with combination and augmentation (Ostroff and Nelson 1999; Barbee et al. 2004; Worthington et al. 2005). Only one 8-week double-blind controlled trial showed significantly greater improvement with the combination of olanzapine and fluoxetine than with either drug alone (Shelton et al. 2001b). See Shelton et al. (2005*) and Corya et al. (2006*) for further double blind RCTs.

2.2 Herbal remedies

For patients who are reluctant to take traditional antidepressants, herbal remedies provide an alternative. There is evidence from a substantial number of controlled trials that suggests that extracts from the plant *Hypericum perforatum* (popularly called St. John's wort) are more effective than placebo for the short-term treatment of mild to moderate depressive disorders (Level A) (Linde and Mulrow 2001

(Cochrane Review); update Linde et al. 2005*). Compared to tricyclic antidepressants and SSRIs, there seems to be no significant difference in treatment response (Linde et al. 2005). However, a placebo-controlled multi-centre trial found no benefits of St. John's wort compared to placebo treatment of patients with moderate to severe major depression (Shelton et al. 2001a). Thus, from the available data, St. John's wort cannot be recommended for the treatment of severe depression (Wernecke et al. 2004).

The standard administered dose of hypericum (St. John's wort) is 600–900 mg/day. Adverse side effects appear to occur less frequently with St. John's wort compared to tricyclic antidepressants (Kim et al. 1999). As yet, little information is available on the herb's medium to long-term efficacy and side effects (AHCPR 1999; Linde and Mulrow 2001). Health care providers should keep in mind that there is evidence that hypericum can interact with a number of prescription drugs (for example, it can decrease blood levels of TCAs and antiretroviral medications used in the treatment of HIV infection, Izzo 2004). In addition, there have been concerns about the purity and variable potency of the herbal remedies.

2.3 Electroconvulsive therapy

Among the indications for electroconvulsive therapy (ECT) as a first-line treatment are: severe major depression with psychotic features, severe major depression with psychomotor retardation, "true" treatment-resistant major depression (see 6.3), refusal of food intake or in other special situations when rapid relief from depression is required (e.g., in severe suicidality or in pregnancy) (American Psychiatric Association 2000). In these cases, referral to specialist psychiatric care and, in most cases, inpatient treatment, should be considered. ECT in treatment-resistant depression was shown in a randomized study to yield significantly more reduction in scores of mood-rating scales compared to paroxetine (Folkerts et al. 1997). In a meta-analysis, ECT was more effective than antidepressant treatment (both compared to TCAs and MAOIs, Pagnin et al. 2004). In general, maintenance treatment is needed, either with medication or ECT.

2.4 Psychotherapy

Though not the main focus of this guideline, psychotherapy plays an important part in the management of depressed patients in primary care. It

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should be considered as an initial treatment modality for patients with mild depression. Further, psychotherapy is recommended in combination with antidepressants for patients with moderate to severe forms of depression and for patients who have had partial responses to antidepressant medications or who have had problems with adherence to antidepressants (Rush and Thase 1999).

Brief, structured psychotherapy sessions have been shown to be effective in the acute-phase treatment of major depression (Frank et al. 2000) and in preventing relapse in the continuation-phase treatment (Jarrett et al. 2001). The best studied psychotherapies efficacious for depression include: cognitive behavioural therapy (CBT) (Rush et al. 1977; Beck et al 1979; Dobson 1989; Gaffan et al 1995; Blackburn and Moore 1997; Glogauen et al 1998; DeRubeis et al 1999; Hollon et al. 1992; Petersen et al. 2004), behavioural therapy (Rehm 1979; Bellack and Hersen 1983; Lewinsohn and Clarke 1984; Nezu 1986; AHCPR 1993; Jarrett et al 1994), interpersonal therapy (IPT) (Klerman et al 1984; Elkin et al 1989; Schulberg et al 1996; Markowitz 2003) and the cognitive behavioural analysis system of psychotherapy (CBASP) (McCullough 2000, 2003). Several of these forms of psychotherapy also appear effective in elderly depressed patients (Hautzinger and Welz 2004; for a systematic review see Hollon et al. 2005). There is less empirical evidence for the efficacy of other types of psychotherapy (for example psychodynamic psychotherapy); however, this does not imply that such treatments are not effective.

Combination of antidepressants and psychotherapy is more effective than the isolated prescription of pharmacotherapy (de Jonghe 2001; Burnand et al. 2002; Jindal and Thase 2003; see Keller et al. 2000 for efficacy in chronic depression). However, one study has shown no advantage of combining antidepressants with psychotherapy (de Jonghe et al. 2004).

Problem-solving treatment (PST) has been shown in one randomized controlled trial to be an effective treatment for depressive disorders in primary care (Mynors-Wallis et al. 2000). In reducing depressive symptoms in elderly people, PST is also an effective treatment option (Alexopoulos 2003). PST can be delivered by non-specialists after training and is, therefore, a cost-effective alternative to formal psychotherapy. It is, however, often not available at all or not promptly enough in the primary care settings of many countries.

When evaluating study data which compare psychotherapeutic and pharmacological treatment, po-

tential bias due to the expectations of the patients and ineffective blinding, as well as insufficient power, have to be considered.

2.5 Light therapy

Seasonal affective disorder (SAD) is a distinct subtype of recurrent major depression that manifests in a seasonal pattern (Rosenthal et al. 1984; American Psychiatric Association 1994a). It is estimated that about 5–10% of the general population, predominantly women, are affected (Kasper et al. 1989; Rosen et al. 1990). “Winter” depression is the most common type of SAD in which patients experience symptoms of clinical depression during the fall and winter, with full remission during the spring and summer seasons.

The first choice treatment of SAD is light therapy where administration is possible and compliance is given (Level A). SSRIs seem to be equally effective but take longer to improve symptoms and induce more side effects (Lam et al. 1995; Ruhrmann et al. 1998; Lee and Chan 1999; Thompson 2002). For detailed reviews, see Golden et al. (2005*) and Pjrek et al. (2005*).

The preferred device for light therapy is a fluorescent light box (which provides white, fluorescent light with ultraviolet wavelengths filtered out) that produces light intensities greater than 2,500 lux. The starting “dose” for light therapy is 10,000 lux for 30–40 min/day, administered each morning for a 2–4-week period. Alternatively, light boxes emitting 2,500 lux require 2 h of exposure per day (Lam and Levitt 1999). Correct positioning (seated close enough to the light box, i.e. no more than 50–80 cm apart, eyes opened) is important. Patients usually show improvement within 1 week, but it can take up to 4 weeks for the full response to be achieved. If a light box is not available, “natural light treatment” may be administered in patients with SAD by a daily 1-hour outdoor morning walk for two or more weeks (Wirz-Justice et al. 1996; Levitt et al 2002).

There are no absolute contraindications to light therapy and no evidence that it is associated with ocular or retinal damage. However, patients with ocular risk factors should have a pretreatment ophthalmological consultation. The common side effects of light therapy reported by patients in clinical trials include eye strain or visual disturbances, headache, agitation, nausea, sedation and, very rarely, hypomania or mania. These side effects are generally mild and transient and resolve with time or with reduction of the light dosage (Lam and Levitt 1999).

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A meta-analysis of studies assessing the efficacy of light therapy in nonseasonal depression did not find an overall statistically significant difference in treatment response compared to control treatment. However, high-quality studies and studies applying morning treatment did show superiority of bright light therapy (Tuunainen et al. 2004 (Cochrane Review)).

2.6 Adjunctive therapy

Interventions intended to provide complementary effects are referred to as adjunctive therapies (Thase et al. 1998). Pharmacological as well as non-pharmacological adjunctive therapies have been suggested for the treatment of major depression (Marangell 2000). Included below is a review of antipsychotics, tranquilizers/anxiolytics, sleep deprivation and exercise training. Many of these treatments may help to reduce anxiety/insomnia and psychotic symptoms until full recovery is achieved.

2.6.1 Antipsychotics. Major depressive disorder may be associated with delusions and/or hallucinations (American Psychiatric Association 2000). Patients with psychotic depression have a considerably better response rate to the combination of an antidepressant plus an antipsychotic than to treatment with either component alone (Level A) (Spiker et al. 1985; Rothschild et al. 1993; Thase 2002; Rothschild 2003; Shelton 2003; Klein et al. 2004). In these patients, it is recommended to combine an antidepressant with an antipsychotic medication when treatment is initiated (Level A). In a recent meta-analysis combining two studies (Spiker et al. 1985; Mulsant et al. 2001) the combination of a tricyclic antidepressant with a classical antipsychotic was more efficient than the tricyclic alone; however, the difference did not reach statistical significance (Wijkstra et al. 2006*). The newer, "atypical" antipsychotics (e.g., amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) may be preferred over the classic antipsychotics (e.g., chlorpromazine, fluphenazine, haloperidol) or clozapine, due to their lower risk of extrapyramidal symptoms (Ostroff and Nelson 1999; Corya et al. 2003; Barbee et al. 2004; Masand 2004). However, the higher risk of metabolic syndrome with atypical antipsychotics should be considered.

There are no controlled data that have compared the "newer" with the "older" antipsychotics in psychotic depression. Usually antipsychotics are administered to depressed patients at lower doses than those used in schizophrenia.

2.6.2 Tranquilizers/anxiolytics. Although tranquilizers (especially benzodiazepines) are frequently used as adjunctive medication in clinical practice worldwide, it is believed by many experts that benzodiazepines in general do not considerably affect the state of mood. Yet a review reported rates for co-administration of an antidepressant and a tranquilizer to be between 30 and 60% of depressed patients in most countries (Furukawa et al. 2001; Valenstein et al. 2004). The reason for this widespread use is most likely the fast onset of action that reduces anxiety, agitation and insomnia in many patients, and the high rate (between 33 and 85% across studies) of anxiety co-morbidity among patients with major depression. In a systematic review, Furukawa et al. (2001) showed that patients with combination treatment of antidepressants and anxiolytics were more likely to show response at 1 and 4 weeks than patients with antidepressant treatment only (although the difference was not longer significant at 6–8 weeks). Benefits of adding anxiolytics have to be balanced against risk of dependence and proneness to accidents.

In each individual patient the potential benefits of adjunctive treatment with benzodiazepines must be carefully balanced against possible harm (including sedation, psychomotor and cognitive impairment, memory loss, potentiation of other central nervous system depressants and treatment-emergent depression, development of dependence and discontinuation syndromes). Predisposed individuals are at greater risk for developing dependency and tolerance; thus, benzodiazepines should not be administered to patients with a history of or current alcohol or drug abuse/dependence. It is also recommended that the duration of benzodiazepine administration in depressed patients be restricted to a maximum period of approximately 4 weeks.

2.6.3 Sleep deprivation. Total or partial sleep deprivation (SD) may be the only antidepressant intervention with marked beneficial same-day effects providing transient amelioration of depression in about 60% of patients (Level A) (Kuks and Tölle 1991; Wirz-Justice and Van den Hoofdakker 1999; Giedke et al. 2003). It is an attractive adjunctive treatment for major depression because it works rapidly, is noninvasive, inexpensive and well tolerated by the majority of patients. However, most patients who do respond subsequently relapse after one night of sleep (Wu and Bunney 1990; Giedke and Schwarzler 2002). Usually, the antidepressant effect can be replicated by repeated total sleep deprivation (Level B) (Wiegand et al. 2001) or by

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combining sleep deprivation with subsequent phase advance of the sleep period (Level D) (Riemann et al. 1999). Bright light therapy has been shown to stabilize the antidepressant effect of partial sleep deprivation (Neumeister et al. 1996).

2.6.4 Exercise training. Studies of healthy young people have shown that physical activity may have positive effects on mood. Open studies of short-term effects of an adjunctive daily aerobic exercise program suggested relatively rapid (after 14 days) mood improvements in patients with major depression (Dimeo et al. 2001). A critical review on this treatment option discussed the potential mechanism of action of exercise (Brosse et al. 2002). The effectiveness of this treatment strategy could not be analysed in a meta-analysis because of a lack of good quality research (Lawler and Hopker 2001). Recently, in a randomized, placebo-controlled study, significant antidepressant effects of walking could be shown in 38 depressed patients (Knubben et al. 2006*).

2.7 Other treatment options

Rapid transcranial magnetic stimulation (rTMS) works via direct stimulation of brain areas through an electromagnetic coil placed near the scalp. Studies evaluating the efficacy of rTMS are heterogeneous regarding the frequency and location of stimulation and show inconsistent results. A recent meta-analysis showed a small benefit compared to sham treatment immediately after 2-week treatment trials (Martin et al. 2003).

Vagus nerve stimulation (VNS) stimulates the brain indirectly via the vagus nerve (cranial nerve X). A generator about the size of a pocket watch is implanted subcutaneously into the left chest wall and is connected to bipolar electrodes that are attached to the left vagus nerve within the neck. Theoretically, activation of the vagus nerve may improve mood via its ascending projections to the amygdala and other limbic structures known to influence emotion and mood (George et al. 2000). There are two small open studies showing response rates of about 30% (Sackeim et al. 2001; Marangell et al. 2002). Data of a sham-controlled trial were published after the date of literature search, essentially showing no difference in response after 10 weeks but increasing response rates for VNS over the year (George et al. 2005; Rush et al. 2005).

3 Continuation-phase treatment of major depressive disorder

The objective of continuation treatment is to decrease the likelihood of relapse in the vulnerable period following symptomatic recovery from depression (i.e. to prevent a return of the current episode of depression) (AHCPR 1993). The continuation phase of treatment is generally considered to be the 6-month period of time immediately following full remission. However, some authors recommend continued treatment for up to 9 months (Reimherr et al. 1998; Hirschfeld 2001; Rush and Kupfer 2001). In general, patients with a history of long previous episodes are candidates for continuation-phase treatment of more than 9 months (Rush and Kupfer 2001). Because residual symptoms (partial remission) are strong predictors of subsequent early relapse, it is recommended to continue treatment until such symptoms have subsided (Paykel et al. 1995).

In placebo-controlled continuation therapy trials, relapse rates ranged from 31 to 80% for those patients who received placebo, compared with only 0 to 31% of those who received active medication (Prien and Kupfer 1986; Prien 1990; Geddes et al. 2003). It is recommended that the same antidepressant successfully used to achieve relief in the acute-phase therapy be continued at the same dose during the *continuation phase* (Level A) (Thase 1999; Rush and Kupfer 2001). If no relapse occurs during continuation therapy, a gradual discontinuation of the antidepressant medication is recommended (Rosenbaum et al. 1998). Patients should be carefully monitored during and immediately after discontinuation to ensure the stability of the remission (American Psychiatric Association 2000). If tapering off results in a return of symptoms, the medication in the original dose should be continued for at least another 6 months before attempting discontinuation again. After a successful course of acute-phase lithium augmentation, combined treatment using an antidepressant and lithium is suggested to be better than the combination of an antidepressant and placebo in the continuation-phase (Bauer et al. 2000; Bschor et al. 2002).

4 Maintenance-phase treatment of major depressive disorder

4.1 General treatment principles of maintenance treatment

4.1.1 Goals and indications. The goals of long-term maintenance (prophylactic) treatment are to prevent

* Published after the date of systematic literature search

a recurrence, suicide and development of chronicity. A recurrence is an episode of depression that appears after a completely asymptomatic period (remission) has been achieved for a 6-month period (recovery) (Frank et al. 1991; Kupfer 1993; Keller 2002). Consideration of the patient's course of illness and treatment history is essential for the implementation of maintenance phase therapy. Even though no definite recommendation can be given as to when prophylactic therapy should be initiated, it is clearly indicated in situations associated with a high risk of recurrence (Brunello et al. 1995; Dawson et al. 1998; Angst 1999a; Hirschfeld 2001; Paykel 2001) (Table IV). Patient preference, severity of functional impairments and side effects experienced during the continuation phase also play a role in determining whether or not maintenance treatment should be implemented (AHCPR 1993; American Psychiatric Association 2000).

4.1.2 Treatment implementation. Key elements of long-term treatment of recurrent depressive disorders include: (1) psychoeducation, (2) pharmacotherapy and (3) adherence monitoring. Because maintenance treatment requires medication compliance, education and a close therapeutic alliance with patients and their families are essential (Kupfer 1993). Strategies to prepare patients and their families for maintenance treatment should include the following topics: typical course of the illness, treatment options, medication effects and side effects, use of (daily) self-reporting instruments to track mood and early warning signs of relapse or recurrence, long-term perspectives and projected end of treatment. It is also important to inform the patient that several different treatments may be necessary before the best individual treatment is identified.

Table IV. Factors associated with increased risk for recurrence in major depressive disorder.

-
- Three or more episodes of major depression
 - High prior frequency of recurrence (e.g., two episodes within 5 years)
 - Previous episode in the last year
 - Residual symptoms during continuation phase treatment
 - Residual subsyndromal symptoms at remission
 - Concurrent dysthymic disorder ("double depression")
 - Severity of episodes (includes suicidality and psychotic features)
 - Longer previous episodes
 - Relapse after medication withdrawal
 - Concurrent coexisting substance abuse
 - Concurrent coexisting anxiety disorders
 - Family history of major depressive disorder in first-degree relatives
 - Onset prior to age 30
 - Age of 60 or 65 and older
-

The frequency of visits may range from monthly visits to every 3–6 months in stable patients and involve (brief) psychiatric evaluation and medication monitoring (e.g., side effect assessment, medication blood levels). In unstable patients, more frequent visits are required. If the patient develops other medical conditions while on maintenance treatment, potential drug–drug interactions should be considered by the treating physician (see Table V). Patients/families should be also educated to inform the treating physician when and if signs of depression reoccur.

4.2 Pharmacotherapy of maintenance treatment

4.2.1 Evidence of efficacy. Pharmacotherapy, especially antidepressant medications and lithium, is the most studied treatment modality in the long-term maintenance treatment of recurrent unipolar depression. The majority of controlled trials investigating these medications in maintenance treatment demonstrated efficacy for relapse prevention (AHCPR 1993, 1999; Solomon and Bauer 1993; Davis et al. 1999; Hirschfeld 2001).

The first choice medications for the treatment of unipolar depression are either the antidepressant with which remission was achieved in the acute/continuation phase or lithium (NIMH Consensus Development Conference 1985; AHCPR 1993; Prien and Kocsis 1995; American Psychiatric Association 2000; Paykel 2001). Likely reasons why antidepressants may be preferred to lithium are that patients are usually treated with antidepressants during the acute/continuation phase and they usually prefer to use medication that does not require regular monitoring by blood tests. Most importantly, the choice of which medication to use depends on how individual patients respond to and tolerate treatment with antidepressants and lithium (Schou 1997). Patients' preference and experience with maintenance treatment should also be considered in the choice of the medication.

4.2.1.1 Antidepressants. Many patients receive antidepressants during the acute and continuation phase. Further, to prevent recurrence of depression the best treatment recommendation is to continue the antidepressant medication that was effective during the acute and continuation phase of treatment at the same dose during the maintenance phase (Level B) (Frank et al. 1993; Franchini et al. 1998; for a systematic review with meta-analysis, see Geddes et al. 2003).

Even mild to moderate side effects during maintenance treatment may lead to noncompliance with the consequence of symptom worsening and increased risk of recurrence. Using medications with a

Table V. Possible interaction of antidepressants with comedications.

Comedication	Interaction
TCAs	
α 1-Adrenoreceptor antagonists (prazosine)	Heightened decrease of blood pressure
Anesthetics/muscular relaxants (halothane, pancuronium, gallamine)	Heightened risk for arrhythmia
Antazids, adsorbants	Possibly lower AD blood levels
Antiarrhythmics (chinine, lidocaine, disopyramide, procainamide, propafenone)	Prolonged intracardiac conduction times, decreased myocardial contraction up to insufficiency
Anticoagulants (warfarin, maybe phenprocoumon)	Heightened effect of anticoagulation with longer bleeding times
Anticonceptives	More side effects of TCAs, lower plasma levels of TCAs observed, therefore lower antidepressive effect possible
Antidiabetics, oral	Higher plasma levels with increased blood sugar decreasing effect
Antimycotics (fluconazole, ketoconazole)	Higher plasma levels of TCAs with more side effects
β -Blocker	Heightened decrease of blood pressure, increase of plasma levels of propranolol and TCAs, therefore more side effects, with propranolol possible worsening or induction of depression
Calcium antagonists (diltiazem, verapamil)	Higher plasma levels of, e.g., imipramine, therefore more side effects
Carbamazepine	Risk of lower plasma level of TCAs because of induction of enzymes (CYP)
Cimetidine	Higher plasma levels with more side effects
Cisapride	Higher plasma levels of antidepressant with higher risk of side effects
Diuretics	Heightened decrease of blood pressure
Insuline	Possibly increased blood sugar decreasing effect
Nicotine, smoking	Lower blood levels of TCAs possible
Omeprazole	Possibly higher plasma levels of TCAs with more side effects
Rifampizine	Lower plasma levels of TCAs, therefore lower antidepressive effect possible
SSRIs	Risk of higher plasma levels of TCAs because of inhibition of enzymes (CYP)
SSRIs	
Antiarrhythmics (propafenone, flecainide)	Inhibition of metabolisation with potentially higher plasma levels of antiarrhythmics
Anticoagulants (phenprocoumon, warfarin)	Fluvoxamine may increase levels of warfarin. Increased bleeding may result.
Antidiabetics, oral	Potentially increased blood sugar decreasing effect of antidiabetics
Antihistaminics (terfenadine, astemizole)	Prolongation of intracardiac conduction times and arrhythmias
β -Blocker	Inhibition of metabolisation of paroxetine, therefore potentially higher plasma levels with higher risk for side effects
Carbamazepine	Risk of higher plasma level of carbamazepine
Cimetidine	Inhibition of metabolisation of paroxetine, therefore potentially higher plasma levels with higher risk for side effects
Cisapride	Higher plasma levels of antidepressant with higher risk of side effects
Digitoxine	Potential lower plasma levels of digitoxine with lower efficacy
Immunosuppressants	Higher plasma levels of immunosuppressants with fluvoxamine and fluoxetine
Theophyllin, coffein	Inhibition of metabolisation of theophyllin with fluvoxamine, therefore higher risk of theophyllin side effects
Tramadole	Risk of central serotonin syndrome
Venlafaxine	
β -Blocker	Inhibition of metabolisation, therefore potentially higher plasma levels with higher risk for side effects
Carbamazepine	Risk of lower plasma level of venlafaxine because of induction of enzymes (CYP)
SSRIs	Risk of higher plasma levels of venlafaxine because of slower metabolisation
Tramadole	Risk of central serotonin syndrome
MAO inhibitors	
Serotonergic drugs (especially SSRIs)	Potentiation of effects and risk of central serotonergic syndrome
Sympathomimetic drugs (epinephrine and other catecholamines, ephedrine)	Risk of hypertensive crisis

more favourable side effect profile than the tricyclic antidepressants may facilitate patient compliance with pharmacotherapy. The “newer” antidepressants are associated with fewer long-term side effects than are the older tricyclics and tetracyclics (AHCPR 1993, 1999; American Psychiatric Association

2000; Peretti et al. 2000; Masand and Gupta 2002).

4.2.1.2 Lithium. The use of lithium as maintenance therapy for unipolar recurrent depression is well established (Level A) (Goodwin and Jamison 1990; Schou 1997; Dunner 1998; Coppen 2000;

Paykel 2001; Fawcett 2003). Two meta-analyses found evidence that lithium is more effective than placebo in preventing recurrence of unipolar depressive illness (Souza and Goodwin 1991; Burgess et al. 2003), but only in one were the results statistically significant (Souza and Goodwin 1991). Over the past decade, evidence has accumulated from retrospective and prospective studies that long-term lithium prophylaxis may reduce suicide risk and even normalize the high mortality rate (Level C) (Coppen et al. 1990; Müller-Oerlinghausen 1992, 1994; Tondo et al. 1997; Schou 2000; Coryell et al. 2001; Tondo et al. 2001; Goodwin et al. 2003).

Serum lithium levels of 0.5–0.8 mmol/l (mEq/l) measured 12 h after last lithium intake are usually recommended for maintenance treatment (Schou 1989). In patients 60 years of age or younger these recommended serum levels are generally achieved with a daily dose of about 12–30 mmol (about 10–20 mmol for Asian patients), and about 6–12 mmol in older patients (see also Birch et al. 1993). There is no difference in efficacy whether lithium tablets are administered once or twice per day. Some patients find a single daily dose facilitates long-term treatment compliance and reduces side effects. In general, extended release forms of lithium are better tolerated.

One advantage of maintenance therapy with lithium is the long and worldwide experience with this agent. Specialized lithium clinics for the prophylactic long-term treatment of patients with affective disorders have been established for more than 30 years in many countries and have provided longitudinal assessments of the side effects of lithium treatment (Schou 1997). Side effects of lithium treatment are usually dose dependent and can often be prevented or relieved by a moderate reduction in dosage (American Psychiatric Association 1994b). Side effects may include: hand tremor (counteracted by a β -blocker), goitre and hypothyroidism (counteracted by additional administration of l-thyroxine [l-T₄] to achieve euthyroid status), lowered renal concentrating ability and polyuria and/or polydipsia (warning against dehydration, possibly reduction of dosage), weight gain (requiring moderate dieting and exercise), gastrointestinal problems such as nausea, dyspepsia, loose stools (managed by administering lithium with meals or switching lithium preparations or dose reduction) and in few cases memory impairment/mental slowness (counteracted by dose reduction) (Birch et al. 1993; American Psychiatric Association 1994b). A small percentage of patients treated with lithium may develop rising creatinine concentrations after 10 years or more of treatment. However, in patients treated with 15 or more years of lithium therapy, affection of both

glomerular and tubular function seems to be more common (Bendz et al. 1994).

During the long-term use of lithium, regular laboratory monitoring of serum lithium levels (three to four times per year and more frequently if clinically required, e.g., in early stages of treatment, with older patients or after clinical changes have become apparent), thyroid function (e.g., TSH level) and renal function (creatinine) (once or twice a year) is recommended (Birch et al. 1993; American Psychiatric Association 1994b; Schou 1997; Kleiner et al. 1999). The purpose of measuring serum lithium levels is to ensure that high serum lithium levels are detected and lowered and to ensure that steps are taken to prevent abnormally low serum levels. It is also important to educate the patients and their families on the warning signs of lithium toxicity.

A relatively small number of studies have directly compared different medications for maintenance treatment in recurrent unipolar depression (Solomon and Bauer 1993). A meta-analysis of studies comparing lithium with other antidepressants showed no conclusive advantage for lithium in the prophylaxis of unipolar illness (Souza and Goodwin 1991). Although the evidence for prophylactic efficacy of carbamazepine in unipolar depression is limited, results indicate that carbamazepine may be an alternative for those patients who do not tolerate or respond to maintenance treatment with lithium or antidepressants (Level C) (Figure 4).

4.2.2 Treatment of symptomatic worsening and recurrence. Brief, mild depressive symptoms (“blips”) frequently occur during maintenance treatment. They are self-limited and, in contrast to recurrences, do not require specific interventions or a change in the maintenance treatment plan. Psychiatric management (e.g., dose adjustment, reassurance) and additional short-term treatment with a benzodiazepine or hypnotic medication to treat insomnia and/or anxiety or an adjunctive course of psychotherapy to help address specific psychosocial stressors may be useful (Rush 1999).

During a prodromal phase of a full-blown recurrence many patients display a somewhat predictable pattern of symptoms. When a patient suffers a recurrence of a depressive episode despite ongoing maintenance treatment (breakthrough episode), physicians face a considerable challenge. Early intervention can shorten the length of the episode (Kupfer et al. 1989). The “differential diagnosis” of a recurrence includes evaluation of occult substance abuse, occult physical illness (e.g., thyroid dysfunction), nonadherence to medication and the possibility of adverse life events (Rush 1999). Patients experiencing a new depressive episode while taking

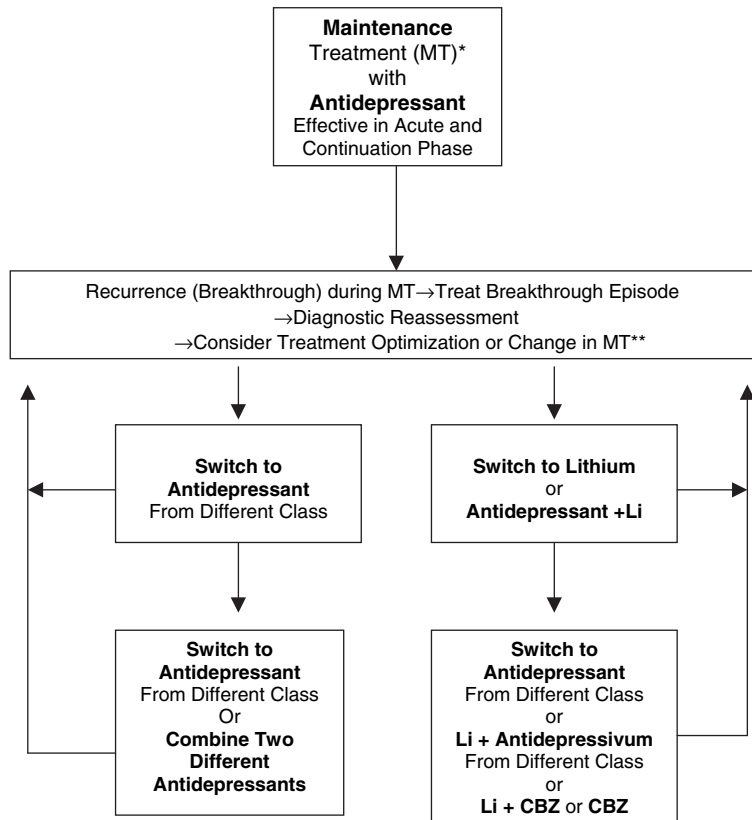


Figure 4. Flow chart: therapeutic options for maintenance treatment of major depressive disorder. CBZ, carbamazepine; MT, maintenance treatment; Li, lithium. *Maintenance electroconvulsive therapy (ECT) is an option for patients responding to ECT in the acute-phase treatment or who fail two or more maintenance medication treatments. **Additional course of psychotherapy may also be considered.

a mood stabilizer or an antidepressant may benefit from treatment optimization (e.g., increase of serum level to the upper end of the therapeutic level, addition of thyroid hormone if thyroid function is low – particularly in lithium-treated patients – additional psychotherapeutic interventions and visits). If the patient does not improve with treatment optimization, another round of adequate acute phase treatment should be initiated followed by continuation treatment (see above).

4.2.3 Maintenance treatment options for prophylaxis-resistant depression. There is growing recognition that prophylactic treatment of affective disorders may be inadequately performed in a substantial proportion of patients. The maintenance treatment of patients who experience recurrences during prophylactic treatment with standard agents, e.g., lithium or antidepressants, is one of the most challenging issues in the treatment of these disorders. However, little data from formal studies is available to guide physicians in the maintenance treatment of patients suffering from recurrences (Bauer and Helmchen 2000). An algorithm including some options for the maintenance treatment of patients with MDD is presented in Figure 4. The possible treatment

options include combining an antidepressant with lithium, combining lithium plus carbamazepine, combining two different antidepressants and ECT (Level D).

4.3 Duration and discontinuation of maintenance treatment

The optimal time to discontinue long-term medication is difficult to predict. Substantial evidence from a controlled 5-year study shows that patients who receive active full-dose medication for at least 5 years benefit the most from continued prophylaxis (Level B) (Kupfer et al. 1992). For some patients, maintenance treatment is required over a long period of time (e.g., a decade) and for others indefinitely (Rush and Kupfer 2001). Three years of maintenance therapy is appropriate almost as a routine for patients with recurrences, particularly where an episode prior to the present one has occurred in the last 5 years or where remission has been difficult to achieve. Maintenance for over 5 years or indefinitely is recommended for those patients at greater risk, particularly where two or three attempts to withdraw medication have been followed by another episode within a year. In clinical practice, antidepressants should always be

tapered off slowly over a 4–6-month period after long-term maintenance therapy to allow the early detection of emerging symptoms and to minimize the risk of discontinuation syndromes. Discontinuation symptoms after abrupt antidepressant cessation have been reported for all drug classes. They are in general mild and brief but can nevertheless be distressing for the patient. They include apart from a high risk for early recurrences (Viguera et al. 1998), e.g., with SSRIs and SNRIs dizziness, ataxia, gastrointestinal and flu-like symptoms as well as sleep disturbances. With lithium, the risk for recurrences after discontinuation seems to be also mainly influenced by the abruptness of the cessation. There is a higher risk for immediate new manic and depressive episodes after lithium discontinuation (Cavanagh et al. 2004), although there is continuing debate about whether this applies to unipolar depressive patients and whether discontinuation might result in decrease in efficacy (see also MacQueen and Joffe 2004). A special discontinuation syndrome has so far not been clearly shown (Schou 1998).

During the period of discontinuation, the patient should be closely monitored. To identify those in whom a relapse is likely after the discontinuation is completed, the monitoring should continue for the next few months (e.g., particularly for the next 6 months, which appear to be a period of high risk for recurrence; Rush and Kupfer 2001). If the full depressive episode recurs during or after discontinuation, the full therapeutic dosage should be promptly readministered (AHCPR 1993). Regardless of the reason for the point in time at which long-term pharmacotherapy is discontinued, the patient should be educated about the risk of recurrence and its early warning signs.

4.4 *Switching from unipolar depression to bipolar disorder*

A change of diagnosis over time from unipolar depression to bipolar disorder has been described in approximately 10–20% of patients (Angst et al. 1978; Akiskal et al. 1995; Solomon et al. 1997). Antidepressants, particularly tricyclics, can precipitate mania in some patients with apparent unipolar depression (Altshuler et al. 1995; Parker and Parker 2003). If a switch to mania occurs during the maintenance phase treatment in unipolar depression, rapid tapering of the antidepressant and concomitant treatment of the manic episode is essential (for more information on the treatment of mania, see *WFSBP Guidelines for the Treatment of Bipolar Disorder*).

4.5 *Psychotherapy*

These guidelines focus on biological (somatic) treatments; therefore, psychotherapeutic treatments alone or in combination with pharmacotherapy will only be mentioned briefly and no levels of evidence are provided. Instead, references for further reading are given.

Maintenance psychotherapy as the sole treatment to prevent recurrence has received less study and at this point is not recommended as a first-line treatment unless the patient does not wish to or cannot take medication for some reason (e.g., pregnancy) (AHCPR 1993). It is, however, a treatment option for some patients. Preliminary data suggest that cognitive behavioural therapy (CBT) may be an effective treatment for preventing recurrence (Teasdale et al 2000; Jarrett et al. 2001; Vos et al. 2004), including in patients who had been successfully treated with antidepressant drugs (Fava et al. 1998). There is some indication that patients with residual depression benefit from CBT for preventing recurrence (Fava et al. 1998; Paykel et al. 1999). Maintenance interpersonal psychotherapy (IPT-M) has also been suggested (Frank et al. 2000; Browne et al 2002). In addition, a cognitive-behavioural analysis system of psychotherapy may provide an alternative maintenance treatment for chronic depression (Klein et al. 2004).

5 **Treatment of chronic depressive disorders**

The most striking characteristics of chronic depressive disorders are undertreatment and social impairment. Patients with chronic depression are often not or inadequately treated (Keller et al. 1995).

5.1 *Dysthymic disorder*

ICD-10 defines dysthymia broadly as a chronic depression of mood which does not currently fulfill the criteria for recurrent depressive disorder in terms of either severity or duration of individual episodes (WHO 1991). Similarly, DSM-IV characterizes dysthymic disorder as a chronic mild depressive syndrome that has been present for two years or longer (American Psychiatric Association 1994a). Individuals with dysthymia frequently have a superimposed major depressive disorder (“double depression”), and those patients are less likely to have a complete recovery compared to patients with major depressive disorder without dysthymia (American Psychiatric Association 2000). However, patients with “double depression” who are treated during a major depressive episode also benefit with respect to their dysthymia (Akiskal 1994; Kocsis 2003).

Dysthymia is a relatively common disorder with a median point prevalence of 2.1% across studies worldwide (Wittchen 2000; Waraich et al. 2004). The lifetime prevalence has been estimated between 3.1% (Weissman et al. 1988) and 6.4% (Kessler et al. 1994). There is epidemiological evidence of high co-morbidity (75%) with other psychiatric disorders, such as major depression, anxiety disorders and substance abuse (Klein and Santiago 2003). Dysthymia (and subthreshold and minor depression) are also common in older adults (Murphy et al. 2002).

5.2 Pharmacotherapy of dysthymic disorder

Although data from controlled studies with antidepressants are still limited, a comprehensive review has confirmed efficacy of various antidepressants in dysthymic disorder (Level A) (World Psychiatric Association Dysthymia Working Group 1995). A recent meta-analysis of 15 randomized controlled trials that used various drugs (mostly antidepressants, TCAs, SSRIs and MAO inhibitors) versus placebo showed that drugs are more effective than placebo, with no difference between and within classes of drugs (De Lima and Moncrieff 2000; De Lima and Hotopf 2003). Although the optimal length of pharmacotherapy in dysthymia has not been studied in a controlled design, a course of treatment with an antidepressant for at least 2–3 years is recommended as in MDD. Better tolerability and side effect profiles compared to the “older” antidepressants (e.g., TCAs) make the SSRIs and other “newer” antidepressants the prime candidates for the long-term treatment of dysthymia (Level A). Amisulpride, a second-generation antipsychotic, showed similar efficacy to the SSRI paroxetine (Rocca et al. 2002) and a higher efficacy than sertraline (Montgomery 2002). Recommended antidepressant doses for dysthymia are similar to those given for acute treatment of a major depressive episode.

There is less evidence regarding the efficacy of antidepressants in dysthymia in older patients. One recent trial suggested that fluoxetine has only limited efficacy compared to placebo and that further research for prediction of response in elderly dysthymic patients is needed (Devanand et al. 2005). An open label trial of venlafaxine suggested a high response rate, although only 18 of 23 patients completed the 12-week treatment (Devanand et al. 2004).

6 Treatment in special circumstances

Under special circumstances the treatment of depression must be modified. These circumstances include depression co-occurring with other psychiatric conditions (anxiety disorders, substance abuse or dependencies), depression in children and adolescents, depression in older adults (where appropriate), depression due to a general medical condition and depression during pregnancy and breast-feeding. In these cases a psychiatric specialist should be involved (see WFSBP guidelines by Bauer et al. 2002a).

6.1 Comorbidity of depression with other psychiatric disorders

6.1.1 Co-morbid anxiety disorders. Up to 30% of unipolar depressive patients suffer from additional anxiety disorders including panic disorder and posttraumatic stress disorder (PTSD) (Wittchen et al. 1999). SSRIs and dual antidepressants (Fawcett and Barkin 1998; Rudolph et al. 1998) but also TCAs and MAO inhibitors can be used effectively. The initial dose should be low (e.g., 5 mg fluoxetine or 10 mg paroxetine) and a gradual increase up to the therapeutic dose should be adapted to the occurrence of side effects. CBT is also effective in treating anxiety disorders co-occurring with depression. Anxiolytics should only be used in the first few days of the episode when severe anxiety is present.

6.1.2 Substance abuse or dependence. Co-morbid substance abuse or dependence is highly prevalent in depression (in 30–60% of patients with abuse/dependence mood and anxiety disorders occur and approximately one-third of patients with mood disorders additionally report times of substance abuse/dependence in their history; Regier et al. 1993; Scott et al. 1998). In primary mood disorders, it is very important to treat both disorders, as co-morbid substance abuse impairs treatment adherence and effectiveness. In some cases treating the substance abuse first should be considered as this could result in decrease of depressive symptomatology. Be aware of possible interactions of antidepressants and, e.g., methadone, where respiratory insufficiency and sedation may occur.

Substance-induced mood symptoms only occur in intoxication and withdrawal (whereas primary depression usually precedes abuse and can be present in abstinence too; American Psychiatric Association 1994). Here, antidepressants should

be given with caution because of a higher risk of unwanted effects. Tailored cognitive psychotherapy proved effective (Scott et al. 1998).

6.2 Treatment of depression in older adults

MDD in late life is more prevalent than previously reported. Underrecognized and undertreated MDD in late life is associated with a poor prognosis (Cole et al 1999; Katona 2000; Steffens et al 2000; Whyte et al. 2004). There are particular challenges in treating older people with MDD effectively and safely. Changes in physiology associated with advancing age produce clinically significant differences in drug metabolism and pharmacokinetics in older versus younger adult patients (Rabheru 2004). Older adults are also more likely to require and receive treatment for co-morbid illnesses, which increases the potential for serious pharmacodynamic and pharmacokinetic drug-drug interactions (Preskorn 1993; Dunner 2003).

There is relatively little data on the use of antidepressants in older patients, especially in the very old (>75 years) and in those with significant medical co-morbidity, dementia or neurological problems (Flint 1998; Roose and Suthers 1998; Roose et al. 2004). Compared to placebo, a systematic review reported TCAs, SSRIs, and mirtazapine to be more effective in patients older than 55 years (Taylor and Doraiswamy 2004). Three meta-analyses of different antidepressant classes in older depressed patients (age >55 or >60) did not show significant differences in antidepressant class with regard to efficacy or tolerability (Mittmann et al 1997; McCusker et al 1998; Gerson et al 1999). Nortriptyline, a secondary amine tricyclic compound, has been the most systematically studied antidepressant in the elderly (Level A) (Flint 1998; Roose and Suthers 1998; Reynolds et al. 2001).

The efficacy and safety of SSRIs in older depressed patients have been evaluated in a number of clinical trials of sertraline, paroxetine and fluoxetine (Level A) (Dunner et al 1992; Tollefson et al 1995; Mulsant et al 1998; Roose and Suthers 1998; Bondareff et al 2000; Muijsers et al. 2002). Venlafaxine and reboxetine have also been shown to be effective in comparative double-blind trials (Katona et al 1999; Staab and Evans 2000) (Level B). Additionally, a meta-analysis found efficacy for moclobemide in geriatric patients (Level A) (Angst and Stabl 1992).

Compared to young adults, response to antidepressant treatment may be slower in older adults (although this only holds for "older" antidepressants [Katona 1994], whereas with SSRIs older patients

may not routinely require longer time to show response [see Sackeim et al. 2005]). Older patients are suggested to be characterized by a higher relapse rate during continuation-phase treatment (Reynolds et al 1996). There is evidence which suggests that older patients may continue to benefit from active continuation-phase treatment. One placebo-controlled trial tested the SSRI citalopram (Klysner et al. 2002) (Level D).

For maintenance treatment there is evidence for efficacy in preventing recurrence compared to placebo for dothiepin (Old Age Depression Interest Group 1993), phenelzine (Georgotas et al. 1989), citalopram (Klysner et al. 2002), and lithium administered in addition to antidepressant treatment (Wilkinson et al. 2003) (Level B).

Cardiovascular side effects are a particular concern in older adults. In a trial comparing paroxetine with nortriptyline use for treatment of depressed patients with ischaemic heart disease, in which a sizable proportion of the patients were older than 60, the two drugs were equally effective for depression, but nortriptyline was associated with a significantly higher rate of serious cardiac adverse effects (Roose et al 1998). Anticholinergic adverse events (e.g., cognitive impairment, constipation, urinary retention) are another important issue in the older population (Table III). Due to the equal efficacy of the various classes of antidepressants, choice of medication is determined by comparing side effect profiles. Because older patients are more prone to orthostatic hypotension and more sensitive to other adverse events such as cardiovascular and anticholinergic effects, SSRIs and the other/newer antidepressants are generally preferred to TCAs (Level A) (Katona 2000; Wilson and Mottram 2004). Older patients are typically started on a lower oral dose than younger adult patients, but it may be necessary to titrate doses for effectiveness. Higher plasma concentrations for a given dose are generally found in older compared to younger individuals (Anderson et al. 2000; American Psychiatric Association 2000) and doses may need to be adjusted particularly in patients with impaired renal or liver function. For a guideline on the management of late-life depression under primary care conditions see Baldwin et al. (2003).

For treatment of dysthymia in older patients see 5.2.

6.3 Treatment-resistant depression

There is no universally accepted definition of treatment resistance. However, if the patient did not respond (according to validated psychometric scales) to at least two treatment trials with different drug

classes (given at a dosage equivalent to 150 mg of tricyclics for a period of 4–6 weeks) treatment resistance is most likely. Since this condition seriously impairs patients, referral to a specialist is recommended (see 2.1.8 for options of treatment optimization; additional psychotherapy or, in severe cases, ECT).

6.3.1 Treatment-resistant depression in older adults.

Treatment-resistant major depression is a common clinical problem in older depressed patients, reported to affect up to one-third of this population. Unidentified co-morbid medical or psychiatric conditions and misdiagnosis often contribute to treatment resistance. Atypical depressive symptoms such as somatic and cognitive symptoms, and co-morbid medical conditions that can themselves produce depressive symptoms, often make it difficult to accurately assess antidepressant response in this age group (Mulsant and Pollock 1998; Katona 2000). Options for treatment-resistant depression in older adults involve reconsideration of the diagnosis, optimizing treatment and use of alternative therapeutic approaches, including switching to another agent, combination therapy and electroconvulsive therapy.

Although there are fewer data than for young adults that support the use of lithium augmentation, lithium seems to be an effective augmenting agent in the treatment of depression in older adults (Level C) (Kushnir 1986; Katona and Finch 1991; Zimmer et al 1991; Uehlinger et al 1995). However, the use of lithium is more problematic in older adults due to less efficient clearance and interaction with concomitant medications (Sproule et al 2000). Regular clinical examination and regular blood level monitoring, aimed at keeping serum lithium levels within the range of 0.4–0.8 mmol/l (mEq/l), enable most older adults to continue lithium treatment safely (Katona and Finch 1991).

6.4 Treatment of depression in children and adolescents

A substantial proportion of patients experience their first episode of major depressive disorder during early childhood, prior to puberty or adolescence (Birmaher et al. 1998). Early-onset MDD is similar in many ways to MDD in adults, but it is a particularly serious form of affective disorder due to the high recurrence rate present at a critical developmental period. Although in these cases referral to a child and adolescent psychiatrist is recommended, a short overview of treatment options is given.

Antidepressants may prove useful in some cases and are especially recommended for patients with

severe depression and psychosis (Birmaher et al 1998). Almost all double-blind controlled trials reported no significant difference in efficacy between TCAs and placebo. The therapeutic role of TCAs (particularly desipramine and imipramine) for children and adolescents must be seriously weighed against lethality of overdose, the possibility of sudden unexplained death (possibly related to cardiac conduction problems; Wilens et al 1996), and the availability of medications which are safer and easier to monitor (Geller et al. 1999). SSRIs appear to have superior efficacy compared to placebo in children and adolescents (Level B) (for fluoxetine, see Emslie et al 1997; for paroxetine, see Keller et al. 2001). The “newer” antidepressants have not yet been studied in RCTs, small open-label studies of venlafaxine (Mandoki et al 1997) and nefazodone (Goodnick et al. 2000) have shown some promising results (Level D). ECT may be considered for acutely suicidal, psychotic or treatment-resistant depression (Thorpe et al. 2001).

As mentioned above, there is discussion regarding an increased risk for suicidal behaviour (including suicidal ideation and attempts) with SSRIs (especially paroxetine, discrepant results for citalopram and sertraline) and newer antidepressants (e.g., venlafaxine) in children leading to official statements of the US Food and Drug Administration (FDA 2005) and the European Medicines Agency (EMA 2005). Therefore, comprehensive information must be given both to patients and parents/legal guardian. If the patient is treated effectively with SSRIs, careful follow-up should be provided. In the case of only partial or non-response, gradual dose reduction under close observation is an option. Abrupt discontinuation of the medication must be avoided.

Given the high rate of relapse of depression, continuation therapy is recommended for all children and adolescents for at least 6 months. As with adults, antidepressants should be continued at the same dose used to attain remission of acute symptoms. At the end of the continuation phase, for patients who do not require maintenance treatment, medications should be discontinued gradually over a period of at least 6 weeks.

6.5 Treatment during pregnancy and breast-feeding

Major depressive disorder occurring during pregnancy is a difficult therapeutic problem (American Psychiatric Association 2000). In contrast to mood stabilizers (lithium, carbamazepine, and valproate), which do have some teratogenicity, antidepressants (TCAs, SSRIs) do not seem to infer increased risk of organ dysgenesis (Altshuler et al. 1996, 2001) and do not increase risk of intrauterine death or major

birth defects (Wisner et al 1999). The (neuro-)development of children whose mothers took TCAs or fluoxetine during gestation did not differ from that of controls (Nulman and Koren 1996; Nulman et al. 1997). Direct drug effects and transient withdrawal symptoms (e.g., jitteriness, tachypnea) occurred in some infants whose mothers were treated with antidepressants near term (Wisner et al. 1999). For “newer” antidepressants, only little information is available. MAO inhibitors are contraindicated during pregnancy due to possible hypertensive crisis. Use of antidepressants during pregnancy is appropriate in many clinical situations, and should include thoughtful weighing of risk of prenatal exposure versus risk of relapse of the mother following drug discontinuation (risk–benefit decision making). Psychotherapy and ECT should be considered as important treatment alternatives. Close monitoring and interventions for patients with identified risks (e.g., poor weight gain) are recommended (Wisner et al. 1999).

Following childbirth, many women are at high risk for the onset or recurrence of a mood disorder. The transient 7–10-day depressive syndrome referred to as “postpartum blues” typically does not meet the criteria for major depressive disorder and does not require medication (American Psychiatric Association 2000). The term “postpartum depression” refers to a major depressive episode occurring within 4 weeks of delivery. Studies have shown a consistent incidence of depression in 10–15% of mothers in the early weeks after delivery (Hoffbrand et al. 2001). Women with a history of MDD have a 25–50% risk of a postpartum depressive episode. Since many women needing antidepressant treatment may wish to breast-feed their infants, several recent studies have identified antidepressants that can be safely used during nursing (Level C) (Wisner et al. 1996; Burt et al. 2001; Hoffbrand et al. 2001). The agents most scrutinized in breast-feeding women are paroxetine, sertraline, fluoxetine, clomipramine and nortriptyline (Stowe et al. 2000; Hendrick et al. 2001). When a psychotropic medication is administered, the infant should be monitored daily by the mother for changes in sleep, feeding patterns and behaviour. The mother should alert the physician if there is any reason for concern.

Update of Guideline

The Guideline will be updated in 2009 to review recommendations and integrate evidence from ongoing trials.

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ORIGINAL INVESTIGATION

Does age at onset support a dimensional relationship between Bipolar II disorder and major depressive disorder?

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Abstract

The current categorical splitting of bipolar and depressive disorders has been questioned. Age at onset is an important variable used to support such a division. Study aim was to assess the distribution of age at onset between bipolar II disorder (BP-II) and major depressive disorder (MDD), and onset age-bipolar family history, onset age-BP-II diagnosis dose–response relationships. No bi-modal distribution and no presence of dose–response relationships would not support a categorical distinction between BP-II and MDD. Consecutive 389 BP-II and 261 MDD major depressive episode (MDE) outpatients were interviewed with the DSM-IV Structured Clinical Interview and the Family History Screen, by a mood specialist psychiatrist in a private practice. Age at onset was defined as age at onset of the first MDE. Distribution of age at onset between BP-II and MDD was studied by Kernel density estimate and histogram methods, dose–response relationships by ROC analysis. BP-II, versus MDD, had significantly lower age at onset, more recurrences, and more bipolar family history. Kernel density estimate and histogram distributions of age at onset showed no bi-modality. Likelihood ratios between age at onset and bipolar family history loading, and between age at onset and BP-II diagnosis, showed dose–response relationships. The bi-modality and dose–response approaches, versus classic diagnostic validators, seem to support a dimensional relationship between BP-II and MDD.

Key words: *Bipolar II disorder, classification, major depressive disorder, unipolar major depression, nosology*

Introduction

Currently, mood disorders are categorically split in bipolar disorders and depressive disorders (American Psychiatric Association 2000; World Health Organization 1992). This division has recently been questioned by the continuum/spectrum concept of mood disorders, which includes overlapping and dimensional disorders ranging from bipolar I (BP-I) and bipolar II (BP-II) disorders to major depressive disorder (MDD) and minor depressions (Angst et al. 2003; Akiskal 2003; Dunner 2003; Cassano et al. 2004; Benazzi 2005a). The continuum/spectrum concept follows Kraepelin's unitary view of mood disorders (including manic/hypomanic states, depressive states, mixed states, and fundamental/temperament states), united in his "manic-depressive insanity" (illness) (Kraepelin 1921). According to Kraepelin, there were "gradual transitions

between the individual forms", and no "sharp boundaries", in mood disorders.

The continuum/spectrum of mood disorders is supported by several findings: (1) mixed states, as the combination of opposite polarity symptoms in the same episode does not support a division between mania/hypomania and depression; (2) factors of mania/hypomania in MDD depression (Hantouche et al. 2003; Benazzi 2004a; Benazzi 2005b; Biondi et al. 2005; Sato et al. 2005); (3) MDD as most common mood disorder in bipolar probands' relatives (Duffy et al. 2000); (4) MDD with bipolar signs closer to bipolar disorders than to "pure" MDD on bipolar validators such as family history and age at onset (Akiskal and Benazzi 2003; Sato et al. 2003; Akiskal et al. 2005; Maj et al. 2006); (5) low diagnostic stability of MDD (Goldberg et al. 2001; Angst et al. 2005a), i.e., many MDD shifting to bipolar disorders in the long run; (6) lifetime

manic/hypomanic symptoms common in MDD (Cassano et al. 2004); (7) no bi-modal distribution of *intradepressive* hypomanic symptoms between BP-II and MDD (Benazzi 2003a); (8) no bi-modal distribution of *lifetime* manic/hypomanic symptoms in MDD and in BP-I (Cassano et al. 2002); (9) no bi-modal distribution of depressive symptoms of mixed mania (Bauer et al. 2005); (10) correlation between *lifetime*, and *intradepressive*, manic/hypomanic symptoms and current depressive symptoms in MDD and BP-II (Cassano et al. 2004; Benazzi 2006a); (11) similar cognitive style patterns in bipolar and unipolar disorders (Jones et al. 2005); (12) lifetime manic/hypomanic symptoms predicting onset of bipolar *and* depressive disorders (Regeer et al. 2006).

The following features could instead support a categorical distinction between bipolar (mainly BP-I) and depressive disorders, on the basis of *differences* on classic diagnostic *validators* (Kendler 1990): (1) family history (Winokur and Tsuang 1996; Coryell 1999; Duffy et al. 2000); (2) age at onset (McMahon et al. 1994; Winokur and Tsuang 1996); (3) gender (Winokur and Tsuang 1996); (4) response to antidepressants, a proxy of biological markers (long-term antidepressants preventing MDD recurrences while probably worsening BP-I course) (Ghaemi et al. 2003; Goldberg and Truman 2003); (4) clinical picture of BP-I depression versus MDD depression (Mitchell and Malhi 2004); (5) course of illness (Winokur and Tsuang 1996).

Age at onset has been shown to be an important and consistent distinguishing feature between bipolar disorders and MDD, being much lower in bipolar disorders (McMahon et al. 1994; Winokur and Tsuang 1996; American Psychiatric Association 2000; Akiskal 2005; Benazzi 2003b). The importance of age at onset in mood disorders goes beyond its utility in separating bipolar disorders and MDD. Age at onset plays a major role in phenotypic distinctions in bipolar disorders and in MDD. Kraepelin (1921) described two peaks of onset of “manic-depressive insanity”, one at age 20 and one at age 50, corresponding to early- and late-onset current subtypes (Shulman 2005). Recently, by complex statistics, three sub-groups with different age at onset have been found in BP-I (Leboyer et al. 2005) and BP-II (Benazzi 2004b), peaking around age 17, 27, and 46. Differences between early- and late-onset BP-I (Leboyer et al. 2005; Shulman 2005), BP-II (Benazzi 2000a,b, 2001), and MDD (Klein et al. 1999; Benazzi 2000b, 2003a), have been found. Early- versus late-onset, BP-I, BP-II, and MDD have been shown to have different clinical picture, long-term outcome, treatment response, mood disorder family loading (higher in early-

onset), and brain biology (more neurological/vascular/cognitive disorders in late-onset). MDD with early onset has been shown to be closer to BP-II than to non-early-onset MDD on several bipolar validators, such as bipolar family history (Benazzi 2003b).

According to Kendell and Jablensky (2003), finding a bi-modal distribution (“zone of rarity”) of some distinguishing features between two related syndromes would support a categorical distinction, while no bi-modality would support a dimensional relation. BP-II is the closest of the bipolar disorders to MDD, and it could be the one to compare to MDD. A bi-modal distribution of age at onset between BP-II and MDD was the expected finding. Instead, no bi-modality could support a continuum/dimensional relationship between the two disorders.

Study aim was to find if there was a continuum/dimensional relationship between BP-II and MDD, by testing the distribution of age at onset between BP-II and MDD, and dose–response relationships between age at onset and bipolar family history loading, and between age at onset and BP-II diagnosis.

Methods

A large database recorded for different study aims was tested. Full details on study methods can be found in previous reports (Benazzi 2003c; Benazzi and Akiskal 2003; Akiskal and Benazzi 2005).

Study setting

An outpatient psychiatry private practice.

Interviewer

A 21-years in practice mood disorder specialist psychiatrist (previously tested inter-rater reliability k for BP-II diagnosis = 0.73) (Benazzi 2003c).

Patient population

Consecutive 389 BP-II, and 261 MDD, major depressive episode (MDE) outpatients. Exclusion criteria: concurrent substance-related disorders, borderline personality disorder, clinically significant medical illnesses, and cognitive disorders.

Study approved by local ethics committee, performed according to ethical standards of 1964 Helsinki Declaration, and all persons gave informed consent prior to inclusion in the study.

Assessment instruments

During the first diagnostic visit the following instruments were used: (1) the Structured Clinical

Table I. Sample features. Bipolar-II disorder (BP-II) versus major depressive disorder (MDD), by univariate logistic regression.

Variables: mean (SD), %	BP-II (<i>n</i> = 389)	MDD (<i>n</i> = 261)	OR (95%CI)
Age, years	41.3 (12.9)	46.8 (14.8)	0.7 (0.6–0.8)**
Females	67.0	61.6	1.2 (0.9–1.7)
Age at onset first MDE	22.8 (10.6)	31.8 (13.8)	0.5 (0.4–0.6)**
Median Age at onset first MDE ≥ 5 MDEs	20	30	<i>z</i> = 8.8, <i>p</i> = 0.0000 2.6 (1.8–3.7)**
Current MDE symptoms >2 years	78.9	58.2	1.1 (0.8–1.5)
Axis I comorbidity	37.5	34.8	1.3 (0.9–1.7)
Psychotic features	54.2	47.5	0.9 (0.5–1.6)
GAF	7.7	8.4	0.9 (0.8–1.0)
Bipolar (type I+type II) Family History	50.2 (9.2)	50.9 (9.6)	4.4 (2.8–7.0)**

MDE, major depressive episode; GAF, global assessment of functioning scale; *z*, statistics of the Mann–Whitney test; OR, odds ratio; 95% CI, 95% confidence intervals.

p* < 0.05; *p* < 0.01.

Interview for DSM-IV Axis I Disorders–Clinician Version (First et al. 1997) (SCID-CV), as modified by Benazzi and Akiskal (Benazzi and Akiskal 2003; Akiskal and Benazzi 2005) to improve the probing for BP-II; (2) the Global Assessment of Functioning scale (GAF, in the SCID-CV) for assessing MDE severity; (3) the Family History Screen (Weissman et al. 2000) for assessing bipolar (type I and II) family history in probands' first-degree relatives. Usually, only BP-I family history is studied because mania is simpler to diagnose than hypomania. Instead, in the present study a lot of effort was made to diagnose hypomania in relatives. Often, family members or close friends supplemented clinical information during the interview.

Definition of age at onset

Age at onset was defined as the age at onset of the first MDE, a reliable definition of onset, while onset of the first hypomania is less reliable (McMahon et al. 1994). Age at onset is subject to recall error. However, there is no reason to think that one group was more likely to have this bias than the other, thus leading to a “non-differential misclassification” (which would reduce, and not increase, any difference) (Rothman and Greenland 1998). Assessment of age at onset of the first MDE is reliable if carried out when depression is not severe, and if there are also key informants, as in the present study (McMahon et al. 1994).

Sample features are presented in Table I.

Testing study aim

If BP-II was a category distinct from MDD, age at onset distribution between BP-II and MDD should be bi-modal (Kendell and Jablensky 2003). Dose–response relationships between age at onset and bipolar family history, and between age at onset and BP-II diagnosis were also tested. If there was a

categorical distinction between BP-II and MDD there would be no dose–response relationship.

Statistics

Logistic regression was used to study associations. Medians were compared by the nonparametric Mann–Whitney *U*-test. The distribution of age at onset between BP-II and MDD was studied by the histogram and by the univariate Kernel density estimation, using the default width of STATA (in order to avoid any possible bias related to the choice of a width more or less likely to show a normal-like distribution). While histograms provide accurate pictures of categorical variables, smooth density functions (Kernel estimators) are better to represent noncategorical variables. Kernel estimators can be regarded as nonparametric histogram smoothers which can reveal skewness and multi-modality. Disadvantages of the histogram method are that it is parametric, and that the fixed bin width results in disproportional representation of density at the center and in the tails of the distribution. For an overview of the Kernel density estimate see Salgado-Ugarte et al. (1994). Nonparametric ROC (receiver-operating-characteristic) analysis was used to test dose–response relationships by likelihood ratios. If BP-II and MDD were disorders not lying along a continuum, there would be no dose–response relationship between age at onset and bipolar family history loading, and between age at onset and BP-II diagnosis. The likelihood ratio expresses the odds that the test result occurs in patients with the disease versus the odds that the test result occurs in patients without the disease. The likelihood ratio for a positive test result (LR+) is the ratio of the probability of a positive test among the truly positive subjects (or the sensitivity) to the probability of a positive test among the truly negative subjects (or the false-positive rate). The likelihood ratio for a negative test result (LR–) is the ratio of the

probability of a negative test among the truly positive subjects (or false-negatives) to the probability of a negative test among the truly negative subjects. In the analyses reported in Tables II and III, the LR – corresponding to each age at onset cut point increases with age at onset, meaning that the higher is age at onset, the lower is the bipolar family history loading (Table II) or the frequency of BP-II diagnosis (Table III). The LR is independent of disease prevalence, making results of more general validity. STATA Statistical Software, Release 8.2, was used (Stata Corporation, College Station, TX, USA, 2003). *P* values were two-tailed, and α level was set at 0.05.

Results

Table I shows the differences between BP-II and MDD reported in several previous reports: BP-II had significantly lower age at onset, more recurrences, and more bipolar family history.

Figure 1 shows the distribution of age at onset between BP-II and MDD by the histogram method. No bi-modality was present.

Figure 2 shows the distribution of age at onset between BP-II and MDD by the Kernel density estimation method. No bi-modality was present.

Table II shows the likelihood ratios of different cut points of age at onset (years, divided by 10) versus bipolar family history loading. The likelihood ratios showed a dose–response relationship.

Table III shows the likelihood ratios of different cut points of age at onset (years, divided by 10) versus the diagnosis of BP-II. The likelihood ratios showed a dose–response relationship.

Discussion

Comparisons between BP-II and MDD showed significant differences on several classic diagnostic validators, such as bipolar family history, age at onset, and recurrences, following previous reports

Table II. Dose–response relationship between age at onset (years, divided by 10) and bipolar family history loading (the higher the LR–, the lower the bipolar family history loading).

Cut point	LR+	LR –
≥2	0.31	1.07
≥2.5	0.30	1.12
≥3	0.31	1.19
≥3.5	0.40	1.25
≥4	0.41	1.41
≥4.5	0.52	1.53
≥5	0.68	1.72
≥5.5	0.88	2.14

LR+, positive likelihood ratio; LR –, negative likelihood ratio.

Table III. Dose–response relationship between age at onset (years, divided by 10) and diagnosis of bipolar II disorder (BP-II) (the higher the LR–, the lower the frequency of BP-II diagnosis).

Cut point	LR+	LR –
≥2	0.22	1.08
≥2.5	0.29	1.14
≥3	0.32	1.19
≥3.5	0.35	1.29
≥4	0.36	1.49
≥4.5	0.44	1.81
≥5	0.55	2.21
≥5.5	0.81	2.45

LR+, positive likelihood ratio; LR –, negative likelihood ratio.

(Winokur and Tsuang 1996; American Psychiatric Association 2000; Mitchell and Mahli 2004). Differences on diagnostic validators could support a categorical distinction between BP-II and MDD, following a classic approach (Kendler 1990).

According to Kendell and Jablensky (2003), the current best approach to the issue of the categorical versus the dimensional classification of mental disorders would be to study if there is a bi-modality in the distribution of some distinguishing features between two related syndromes. A feature consistently shown to distinguish bipolar disorders and depressive disorders is age at onset (much lower in bipolar disorders). The distribution of age at onset was expected to be bi-modal, because of the reported BP-MDD differences. Instead, in the present study no bi-modal distribution of age at onset was found between BP-II and MDD. The finding could support a continuum/dimensional relationship between BP-II and MDD. This finding was further supported by the dose–response relationships found between age at onset and bipolar family history loading, and between age at onset and BP-II diagnosis. No relationship should have been found if BP-II and MDD were distinct, categorical disorders.

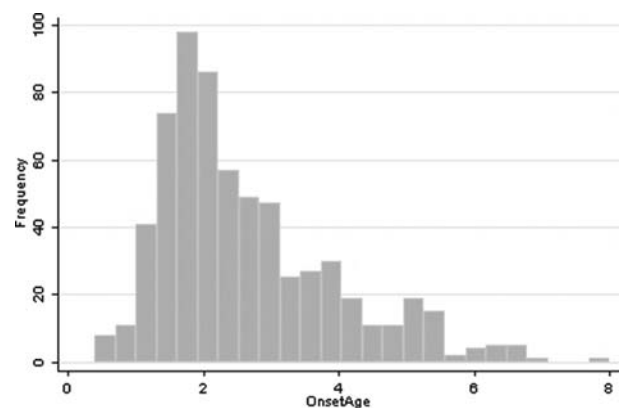


Figure 1. Histogram of the distribution of age at onset (years) between Bipolar II Disorder and Major Depressive Disorder.

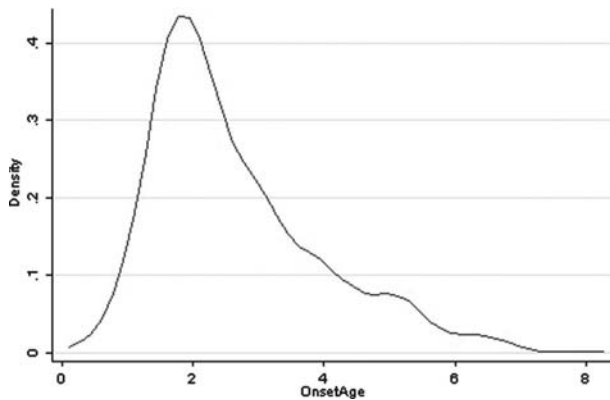


Figure 2. Kernel density estimate of the distribution of age at onset (years) between Bipolar II Disorder and Major Depressive Disorder.

Interpretation of study findings relies on the method used to define a categorical disorder. By using classic diagnostic validators, BP-II and MDD would seem to be distinct disorders. By using the bi-modality (“zone of rarity”) approach, a continuum/dimensional relationship between BP-II and MDD would seem to be supported. A continuity between BP-II and MDD would also seem to be supported by the dose–response relationship found between age at onset and bipolar family history loading, and between age at onset and BP-II diagnosis.

These results complement recent studies testing the MDD/BP-II continuity on different variables (Akiskal and Benazzi 2006; Benazzi 2006a–d), reporting: (1) a correlation between intradepressive hypomanic symptoms and depressive symptoms; (2) a dose–response relationship between depressive symptoms and mixed depression (i.e. an MDE plus three or more intradepressive hypomanic symptoms); (3) a dose–response relationship between number and scores of intradepressive hypomanic symptoms and bipolar family history loading; (4) no bi-modality in the distribution of the number and scores of intradepressive hypomanic symptoms between BP-II and MDD; and (5) no bi-modality in the distribution of the number of the mood/behaviour instability items of cyclothymic temperament and of borderline personality between BP-II and MDD. These findings are probably related to the significant proportion of MDD with bipolar signs (such as early age at onset, many recurrences, bipolar family history, atypical depression, mixed depression) (Winokur and Tsuang 1996; Ghaemi and Goodwin 2002; Sato et al. 2003; Akiskal and Benazzi 2003; Cassano et al. 2004; Akiskal 2005; Akiskal et al. 2005; Benazzi 2005b; Biondi et al. 2005; Maj et al. 2006), which could bridge the gap between BP-II and “pure” MDD. The MDD subgroup with bipolar signs has been shown to be

closer to BP-I and BP-II than to “pure” MDD on bipolar validators such as bipolar family history and young age at onset (Akiskal and Benazzi 2003; Sato et al. 2003; Akiskal et al. 2005; Benazzi 2005b; Maj et al. 2006).

Limitations

A single interviewer may have limited the validity of the findings. The validity of the interview may be supported by: (1) the semi-structured interviewing (Dunner and Tay 1993; Brugha et al. 2001; Aalto-Setälä et al. 2002; Simpson et al. 2002; Benazzi 2003d); (2) the systematic assessment by validated instruments; (3) the interviewer’s training on BP-II diagnosis; (4) the interview of key informants; (5) analysis of a database recorded for different study goals. Further supporting the interview method are the close similarities found between a present setting BP-II sample and the BP-II sample of an independent group (Angst et al. 2005b), and the differences in age at onset between BP-II and MDD replicating previous reports (McMahon et al. 1994; Winokur and Tsuang 1996; Mitchell and Malhi 2004; Akiskal 2005).

Statement of interest

The author has no conflict of interest with any commercial or other associations in connection with the submitted article.

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ORIGINAL INVESTIGATION

Mirtazapine monotherapy versus combination therapy with mirtazapine and aripiprazole in depressed patients without psychotic features: A 4-week open-label parallel-group study

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Abstract

Background: There is preliminary evidence that the atypical antipsychotic aripiprazole, which is a partial agonist at D₂ and 5-HT_{1A} receptors and a potent antagonist at 5-HT_{2A} receptors, may be useful as an augmentation strategy in treatment-resistant depression.

Method: In this 4-week open-label non-randomized parallel-group study, the safety and efficacy of aripiprazole as add-on treatment strategy in patients suffering from non-delusional depression was investigated. Forty drug-free depressed inpatients without psychotic symptoms (13 men, 27 women), suffering from a major depressive episode or bipolar disorder, depressive state (DSM-IV criteria), were included in the study. The patients were treated either with mirtazapine monotherapy (45 mg/day) or combination therapy (mirtazapine 45 mg/day plus aripiprazole 15 mg/day) for 4 weeks. Safety and efficacy were assessed weekly using the Hamilton Depression Rating Scale, the Simpson–Angus Scale and the Barnes Akathisia Scale.

Results: Mirtazapine monotherapy and combined treatment with mirtazapine and aripiprazole showed comparable antidepressant effects as assessed at the endpoint of the study period. However, additional administration of aripiprazole accelerated the onset of antidepressant action in patients suffering from treatment-resistant depression. Additive use of aripiprazole reduced the mirtazapine-induced increase in the body mass index. Moreover, mirtazapine had favourable effects on aripiprazole-induced akathisia. No other extrapyramidal side effects were seen in the combination therapy group.

Conclusion: Combined therapy with mirtazapine and aripiprazole is a safe and well-tolerated treatment option which may be useful especially in treatment-resistant depression. Double-blind controlled studies are needed to further explore the efficacy and safety of aripiprazole in depressed patients.

Key words: Antidepressants, atypical antipsychotics, major depressive disorder

Introduction

In contrast to classical antipsychotics such as haloperidol, which are strong D₂ receptor blockers and may induce depressive symptoms (Awad 1993; Browne et al. 1998; Helmchen and Hippus 1967), atypical antipsychotics apparently have genuine antidepressant effects due to their specific biochemical properties such as limbic selectivity of antidopaminergic effects, blockade of presynaptic autoreceptors, fast dissociation from the dopamine D₂ receptor, serotonin 5-HT_{2A} receptor blockade, or serotonin 5-HT_{1A} receptor agonism (Blier and

Szabo 2005; Moller 2005; Yatham et al. 2005). Some atypical antipsychotics such as zotepine or ziprasidone are even shown to have norepinephrine and/or serotonin reuptake inhibiting effects (Stahl and Shayegan 2003; Tatsumi et al. 1999) which may also account for antidepressant efficacy. Therefore, the use of various atypical antipsychotics in the treatment of depressive symptoms is not restricted to psychotic features in delusional depression, but is obviously also efficacious in depressive disorder without psychotic symptoms (Amore and Jori 2001; Calabrese et al. 2005; Cassano and Jori 2002; Shelton et al. 2001; Tohen et al. 2003).

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Aripiprazole, a novel atypical antipsychotic agent, has a pharmacological profile that is different from any of the other typical or atypical antipsychotic agents currently available. It acts as a potent partial agonist at dopamine D₂ receptors and at serotonin 5-HT_{1A} receptors, and as a potent antagonist at 5-HT_{2A} receptors (Burriss et al. 2002; Jordan et al. 2002). Aripiprazole has a mean elimination half-life of approximately 75 h and it is primarily eliminated by hepatic metabolism via multiple biotransformation pathways including both cytochrome CYP3A4 and 2D6 (Bowles and Levin 2003). The risk of aripiprazole to induce extrapyramidal motor side effects appears comparable to that of placebo and much lower than that of haloperidol, although akathisia may increase during aripiprazole treatment (Marder et al. 2003). Apart from the occasional induction of akathisia, aripiprazole has a markedly good safety and tolerability profile, especially with regard to weight, prolactin, QTc interval changes, glucose and lipid metabolism (Fleischhacker 2005).

Aripiprazole has been demonstrated to be clinically effective in schizophrenia (Kane et al. 2002; Potkin et al. 2003) and in acute mania (Keck et al. 2003; Sachs et al. 2006; Vieta et al. 2005). There is also evidence from preclinical and clinical studies that aripiprazole possesses antidepressant effects: From a theoretical point of view, the partial agonistic effects of aripiprazole on D₂ and 5-HT_{1A} receptors as well as the antagonistic impact at 5-HT_{2A} receptors suggest antidepressant efficacy, because regulation of dopaminergic neurotransmission appears to be associated with depressive symptoms (Willner et al. 2005) and dopamine agonists such as pramipexole (Goldberg et al. 2004; Lattanzi et al. 2002; Zarate et al. 2004) or bromocriptine (Wada et al. 2001) may exert antidepressant effects in depressed patients. Furthermore, a relationship between 5-HT_{1A} agonism of atypical antipsychotics and improvement in depressed mood has been postulated (Millan 2000; Richelson 1999). Finally, potent 5-HT_{2A} receptor antagonism coupled with weak D₂ receptor blockade is regarded as a possible mechanism of atypical antipsychotics in alleviating depressive symptoms in different psychiatric disorders (Meltzer et al. 2003; Moller 2005). Moreover, under clinical conditions in populations with schizophrenia, aripiprazole significantly reduces depressive symptoms both during acute and during maintenance therapy (Carson and Kitagawa 2004; Kasper et al. 2003; Kujawa et al. 2002; McQuade et al. 2002). Furthermore, there are also several open-label trials in treatment-resistant depressive patients or depressed patients with residual anxiety symptoms suggesting antidepressive effects of aripiprazole if this drug is given additionally to treatment with

various antidepressants (Barbee et al. 2004) or with SSRIs (Adson et al. 2005; Papakostas et al. 2005; Simon and Nemeroff 2005; Worthington et al. 2005). However, in none of these open-label trials a parallel group was included and all depressive patients were pre-treated with diverse antidepressants (mostly SSRIs), receiving aripiprazole as additional treatment. Therefore, it is impossible to separate augmentation drug response to aripiprazole from clinical response due to continued administration of the respective antidepressant in these trials, and therefore the conclusions which can be drawn from these studies are limited.

The present 4-week open-label study is the first parallel-group trial investigating the safety and efficacy of additional aripiprazole treatment in depressed patients. Mirtazapine was chosen as standard antidepressant, because former aripiprazole studies in depressive patients focussed on SSRIs and combination therapy using mirtazapine and aripiprazole has not been investigated so far. The antidepressant mirtazapine does not inhibit the reuptake of norepinephrine or serotonin but acts as an antagonist of α_2 , 5-HT₂, 5-HT₃, and histamine H₁ receptors, increasing serotonergic neurotransmission via an enhancement of 5-HT cell firing and a blockade of α_2 -adrenergic heteroreceptors at the 5-HT nerve terminals (De Boer 1995). These indirect mirtazapine-induced serotonergic effects may be further enhanced by additional treatment with aripiprazole. Moreover, mirtazapine has been shown to effectively reduce antipsychotic-induced akathisia (Poyurovsky et al. 2006) and may therefore be more convenient than SSRIs when given in combination with aripiprazole. In the present investigation, monotherapy with mirtazapine was compared with combination treatment (mirtazapine, aripiprazole) after a wash-out period of at least 3 days. In contrast to previous studies, aripiprazole was used in the combination therapy group from the very beginning and not as a secondary augmentation strategy in pre-treated patients. Depressed patients both with and without treatment resistance were included in the study. Patients suffering from depression with psychotic features were excluded from the study in order to analyse possible genuine antidepressant effects of aripiprazole in non-delusional depression. A 4-week study period was regarded to be sufficient since efficacy of antidepressant drugs is expected to become obvious within the first 2 weeks in most cases (Posternak and Zimmermann 2005; Stassen et al. 1996; Szegedi et al. 2003) and in particular dual-action antidepressants such as mirtazapine may have a faster onset of action (Bech 2001; Nierenberg 2001; Quitkin et al. 2001; Stahl et al. 2001; Thompson

2002). The aim of the present study was to investigate the tolerability and safety of combination therapy with mirtazapine and aripiprazole and secondly to gain first preliminary evidence regarding the efficacy of this combination in depressed patients. Due to the open-label design and the small sample size, it was not our goal to arrive at a closing evaluation of efficacy of this combined treatment, but to give helpful suggestions for future double-blind placebo-controlled trials.

Materials and methods

Study design

In this 4-week open-label, non-randomized, parallel group study, the safety and efficacy of aripiprazole as add-on treatment strategy was investigated in 40 depressed patients without psychotic features. Combination treatment with mirtazapine and aripiprazole was compared with mirtazapine monotherapy. The study was carried out at the Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University of Munich, between July 2004 and December 2005. The trial was performed according to the Declaration of Helsinki (www.wma.net) and The International Conference on Harmonisation (ICH)/Good Clinical Practice guidelines (www.ich.org) and had been approved by the local ethics committee. All patients provided written informed consent before participation in this study.

Patient population

Forty drug-free depressed inpatients (13 men, 27 women) aged between 22 and 76 years (mean age 47.50 ± 14.29 years) entered the study after the procedures had been fully explained and written informed consent had been obtained. The patients were diagnosed by experienced and trained psychiatrists according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria (American Psychiatric Association 1994) using the Structured Clinical Interview for DSM-IV, German version (Wittchen et al. 1997).

Inclusion criteria for the depressed patients were: (a) a major depressive episode or bipolar disorder, depressive state, according to DSM-IV criteria; (b) a sum score of at least 18 on the 21-item version of the Hamilton Depression Rating Scale (21-HAMD) (Hamilton 1960); (c) availability of normal laboratory parameters; normal electrocardiogram; and normal encephalogram. Exclusion criteria were: (a) occurrence of psychotic symptoms (psychotic depression not included); (b) major medical disorders; (c) substance dependence or substance abuse (except for nicotine) within 12 months prior to screening; (d)

other comorbid Axis I disorders according to DSM-IV; (e) pregnant or breast-feeding female patients.

Further clinical characteristics are given in Table I.

Study medication and determination of mirtazapine and aripiprazole serum concentrations

Patients were assigned at the discretion of the doctor in attendance to one of the two treatment groups: monotherapy (mirtazapine 45 mg/day for 4 weeks) or combination therapy (mirtazapine 45 mg/day plus aripiprazole 15 mg/day for 4 weeks). 20 depressed patients were treated with monotherapy, 20 patients with combination therapy. Mirtazapine was given in both treatment groups using the following dosing schedule: (a) day 0: 0–0–0–15 mg; (b) day 1: 15–0–0–15 mg; (c) day 2 up to end of the study: 15–0–0–30 mg. The aripiprazole dosage (15 mg/day orally in the morning) was not titrated and was dispensed in the combination therapy group only, beginning on day 1 up to day 28.

The mirtazapine and aripiprazole concentrations were measured weekly at 08:00 h by means of an isocratic reversed-phase high-performance liquid chromatography (HPLC) separation and ultraviolet (UV) detection at 214 nm, as described earlier (Schüle et al. 2006).

Prior and concomitant medication

Patients were required to discontinue all psychotropic medications for at least 3 days before study start. Concomitant treatment with other psychoactive drugs was prohibited, except for zopiclone (up to 7.5 mg/day at night) in case of sleep difficulties and lorazepam (up to 3 mg/day) in case of inner tension, anxiety or agitation.

Out of the 40 patients included in the study, 13 patients did not receive any psychopharmacological pre-treatment and were drug-free for at least 35 days when entering the study. None of the patients had been pre-treated with fluoxetine (long half-life), mirtazapine, or aripiprazole during the current episode. Eight patients had been pre-treated with tricyclic antidepressants, 10 patients with selective serotonin reuptake inhibitors (SSRIs), four patients with reboxetine, four patients with venlafaxine, and one patient with opipramole. Treatment-resistant depression (TRD) before entering the study was defined as failure to respond to at least two trials of antidepressants at an adequate dose and duration from at least two different classes (Ananth 1998). In each patient the occurrence of TRD was verified by performing a thorough psychiatric exploration and

Table I. Baseline demographics and illness characteristics of depressed patients treated with monotherapy (mirtazapine 45 mg/day) or combination therapy (mirtazapine 45 mg/day and aripiprazole 15 mg/day) over 4 weeks.

Characteristic	Monotherapy (n = 20)	Combination therapy (n = 20)	Statistical evaluation		
			χ^2	df	P
Diagnosis (MD vs BD)	19 MD, 1 BD	18 MD, 2 BD	–	–	1.000 ^a
No pre-treatment (at least 35 days)	8/20	5/20	–	–	0.501 ^a
TRD (≥ 2 trials before)	6/20	9/20	0.960	1	0.327
First depressive episode	10/20	4/20	–	–	0.096^a
Gender (M/F)	4 M, 16 F	9 M, 11 F	2.849	1	0.091
			<i>F</i>	df	<i>P</i>
Age	50.30 \pm 15.63	44.70 \pm 12.58	1.558	1, 39	0.220
Height	167.60 \pm 8.70	170.35 \pm 9.63	0.898	1, 39	0.349
Weight	68.82 \pm 15.90	78.70 \pm 21.32	2.759	1, 39	0.105
BMI	24.29 \pm 4.05	26.99 \pm 6.05	2.760	1, 39	0.105
Age of onset (years)	40.95 \pm 16.82	34.85 \pm 10.27	1.917	1, 39	0.174
Number of depressive episodes	2.30 \pm 1.81	3.00 \pm 2.34	1.120	1, 39	0.297
Duration of illness (years)	6.14 \pm 8.01	9.78 \pm 10.26	1.557	1, 39	0.220
Duration of index episode (days)	115.50 \pm 111.35	189.40 \pm 178.72	2.463	1, 39	0.125
Duration of wash-out period (days)	16.50 \pm 15.64	11.00 \pm 14.22	1.355	1, 39	0.252
Baseline 21-HAMD sum score	23.45 \pm 4.27	24.75 \pm 5.40	0.719	1, 39	0.402
Baseline SAS sum score	2.15 \pm 3.66	0.90 \pm 2.55	1.569	1, 39	0.218
Baseline BAS sum score	0.70 \pm 1.38	0.65 \pm 0.99	0.017	1, 39	0.896

Data represent mean \pm SD (standard deviation). Statistical evaluation: χ^2 -test or Fisher's exact test (qualitative variables), one-way ANOVA (quantitative variables). Df, degrees of freedom; MD, major depression (unipolar); BD, bipolar disorder, depressive state; TRD, treatment-resistant depression; M, males; F, females; BMI, body mass index; 21-HAMD, Hamilton Depression Rating Scale, 21-item version; SAS, Simpson–Angus Scale; BAS, Barnes Akathisia Scale. Significant results ($P < 0.05$) and statistical trends ($P < 0.10$) in bold letters.

^aFisher's exact test (two-sided).

by evaluating the medical reports of the admitting psychiatrist.

Efficacy evaluations

Severity of depression was estimated weekly (days – 1, 7, 14, 21, 28) using the 21-HAMD in the morning between 09:00 and 11:00 h. Clinical response was defined by a reduction of at least 50% in the 21-HAMD sum score after 4 weeks of treatment. Remission was defined as a score ≤ 7 in the 21-HAMD sum score at week 4 (Thase et al. 2001).

Extrapyramidal side effects were estimated weekly using the Barnes Akathisia Scale (BAS) and the Simpson–Angus Scale (SAS). The BAS is a four-item, clinician-administered instrument designed to measure drug-induced akathisia and includes objective akathisia, subjective awareness of restlessness, subjective distress related to restlessness, and global clinical assessment of akathisia (Barnes 1989). The SAS is a 10-item scale to assess parkinsonism and drug-related extrapyramidal side effects (Simpson and Angus 1970). In addition, the patients were physically examined weekly. All side effects and adverse events reported by the patients or observed by the examiners were recorded using a four-point

scale to estimate the severity (0 = none, 1 = mild, 2 = moderate, 3 = severe). Blood pressure (in supine position), heart rate and laboratory parameters were also measured weekly. At the beginning and the end of the study (day – 1, day 28), an electrocardiogram (ECG) was performed.

All raters were experienced psychiatrists or psychologists and familiar with the psychometric measurement instruments.

Statistical analyses

Homogeneity at baseline in clinical and demographic variables between the monotherapy and combination therapy group was analysed by the χ^2 -test for contingency tables or Fisher's exact test with respect to qualitative variables or by one-way ANOVA procedure with regard to quantitative variables.

Response and remission rates were compared between both treatment groups using the χ^2 -test for contingency tables. The duration of the inpatient stay was compared by means of the two-sided *t*-test for independent samples. For the statistical evaluation of efficacy parameters (21-HAMD), safety parameters (weight, body mass index = BMI, BAS, SAS), dosages of concomitant medication

(lorazepam, zopiclone), and mirtazapine concentrations, analyses of variances (ANOVAs) with a repeated-measures design were performed. Thereby “time” (week 0–4) and “group” (monotherapy versus combination therapy) were considered as within-subjects and between-subjects factors with five (“time”) and two (“group”) levels, respectively. For the ANOVA procedures, a correction was applied to the F value by means of adjusting the degrees of freedom by a factor Epsilon, if the sphericity test (Mauchly W -test) was significant indicating an heterogeneity of covariances (Huyn-Feldt correction).

To analyse the time course of clinical response and to compare the time until response (at least 50% reduction in 21-HAMD sum scores) between the two treatment groups, survival analysis and the Kaplan–Meier product limit estimate were used (Kaplan and Meier 1958). Moreover, the time until response was compared by means of survival analysis between depressed patients with and without treatment resistance before entering the study, separately for both treatment groups (monotherapy, combination therapy). Comparisons of the survival curves were performed using the Log-Rank test.

Statistical analysis was performed using SPSS for Windows (Release 12.0.1, SPSS Inc., Chicago, IL 60606, USA). As a nominal level of significance, $\alpha = 0.05$ was accepted. A statistical trend was defined by $0.05 < P \leq 0.10$. Due to the explorative nature of this pilot study, an adjustment of α , e.g., according to Bonferroni procedure, was not carried out.

Results

Patients

After a total of 52 depressed inpatients had been screened, 42 fulfilled study criteria and agreed to participate in the study. Two female patients had to be excluded from the study during the first week of treatment, because there was a pronounced elevation of liver enzymes or a switch into mania, respectively. These two patients were not considered in the analysis of the data, since only the baseline ratings were available. The remaining 40 patients were assigned to the both treatment groups at the discretion of the doctor in attendance. 20 patients were treated with mirtazapine monotherapy, 20 patients received combination therapy (mirtazapine, aripiprazole). None of these 40 patients dropped out during the 4-week treatment period. Three out of 40 patients suffered from bipolar depression (one in the monotherapy group, two in the combination therapy group). None of the three bipolar depressed patients was treatment-resistant before entering the study.

Regarding the clinical and demographic characteristics at baseline, there was a trend for higher proportions of recurrent depressive episodes ($P = 0.096$) and male patients ($P = 0.091$) in the combination therapy group. No other significant differences or statistical trends were observed with respect to all other clinical and demographic variables, although patients receiving combination therapy were prone to have a somewhat higher proportion of treatment resistance, a lower age of onset, and a longer duration of the index episode (Table I).

Antidepressant efficacy

Eleven out of 20 (55.0%) depressed patients were responders to 4-week mirtazapine monotherapy, whereas 12 out of 20 (60.0%) patients responded to the combination of mirtazapine and aripiprazole after 4 weeks of treatment. No significant difference in the response rates between both treatment groups was seen ($\chi^2 = 0.102$; $df = 1$; $P = 0.749$). Moreover, the remission rates were comparable in both treatment groups (monotherapy group: four out of 20 patients [20.0%]; combination therapy group: five out of 20 [25%]; Fisher’s exact test: $P = 1.000$). The duration of the inpatient stay was somewhat higher in the monotherapy group (54.25 ± 40.50 days) than in the combination therapy group (46.90 ± 18.79 days) without reaching statistical significance ($T = 0.736$; $df = 38$; $P = 0.466$). The only patient out of the monotherapy group who suffered from bipolar depression was a responder to mirtazapine monotherapy and was additionally treated with lamotrigine after finishing the 4-week study period.

For the 21-HAMD sum scores, repeated-measures ANOVA revealed a highly significant “time” effect in the overall patients group ($F = 71.888$; $df = 3.354$, 127.468; $P < 0.001$), suggesting a significant decrease in severity of depression during the 4-week treatment period (Figure 1A). However, there were no significant “time” \times “group” interactions ($F = 0.238$; $df = 3.354$, 127.468; $P = 0.889$) and no significant “group” differences ($F = 0.152$; $df = 1$, 38; $P = 0.699$), indicating that both treatment strategies (monotherapy, combination therapy) were equally effective in reducing depressive symptoms.

Kaplan–Meier survival analysis

The mean duration of treatment until response (at least 50% reduction in 21-HAMD) was comparable in both treatment groups: (a) monotherapy: 3.350 ± 0.118 weeks, 95% CI: 3.118–3.582 weeks; (b) combination therapy: 3.334 ± 0.117 weeks, 95% CI: 3.106–3.563 weeks; log-rank test: $\chi^2 = 0.08$; $df = 1$; $P = 0.7760$; Figure 2A). Treatment-resistant

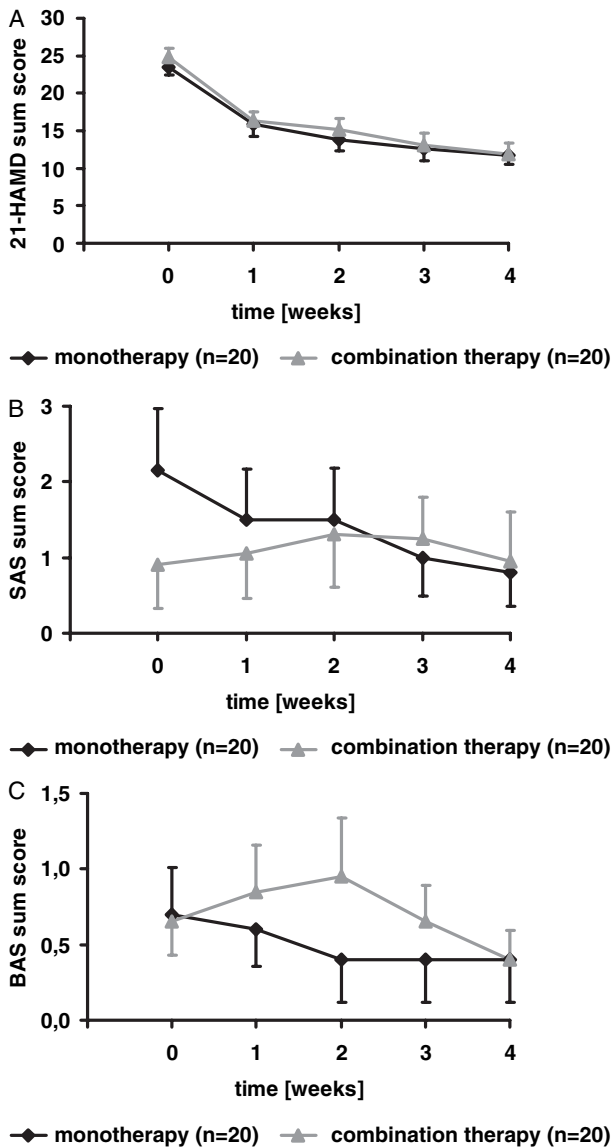


Figure 1. 21-HAMD (A), SAS (B) and BAS (C) sum scores in depressed patients treated with monotherapy (mirtazapine 45 mg/day; $n=20$) or combination therapy (mirtazapine 45 mg/day and aripiprazole 15 mg/day; $n=20$) on week 0 up to week 4. Data represent the mean \pm SEM. Significant results ($P < 0.05$) in repeated-measures ANOVAs are indicated (time, time \times group, and group effects). 21-HAMD, Hamilton Depression Rating Scale; SAS, Simpson–Angus Scale; BAS, Barnes Akathisia Scale.

depression (TRD; two or more treatment trials without success before the study) had a significant impact on the time course of response in the monotherapy group, but not in the combination therapy group (Figure 2B,C). Regarding the monotherapy group, the mean time until response was significantly longer in patients with TRD than in patients without TRD: (a) TRD: 3.693 ± 0.188 weeks, 95% CI: 3.325–4.061 weeks; (b) no TRD: 3.213 ± 0.147 weeks, 95% CI: 2.925–3.502 weeks; log-rank test: $\chi^2 = 5.18$; $df = 1$; $P = 0.0229$; Figure 2B). On the contrary, in the combination therapy

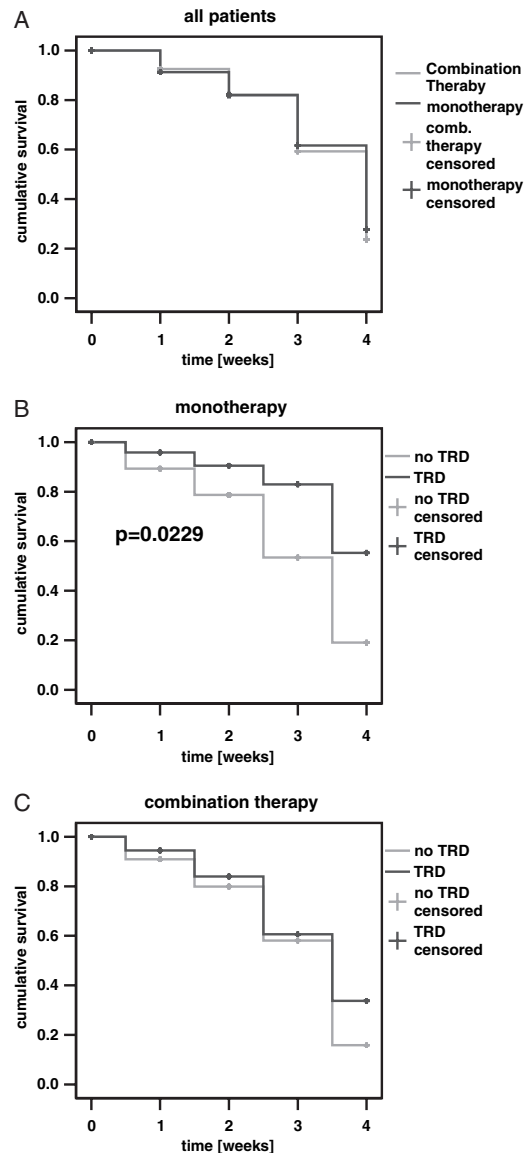


Figure 2. Kaplan–Meier survival analysis of time until response. (A) Comparison between monotherapy group ($n=20$) and combination therapy group ($n=20$) in all patients. (B) Comparison between patients with ($n=6$) and without ($n=14$) treatment-resistant depression (TRD) in the monotherapy group. (C) Comparison between patients with ($n=9$) and without ($n=11$) TRD in the combination therapy group. Censored cases: no response up to the end of the observation period (week 4).

group the mean time until response did not differ significantly between patients with and without TRD: (a) TRD: 3.390 ± 0.170 weeks, 95% CI: 3.057–3.724 weeks; (b) no TRD: 3.289 ± 0.164 weeks, 95% CI: 2.968–3.610 weeks; log-rank test: $\chi^2 = 0.78$; $df = 1$; $P = 0.3778$; Figure 2C).

Concomitant medication, mirtazapine concentrations

The dosages for both lorazepam ($F = 7.379$; $df = 1.411$, 53.605; $P = 0.004$) and zopiclone ($F = 5.666$; $df = 1.778$, 67.548; $P = 0.007$) significantly

decreased during the 4-week treatment period. Neither significant “time” × “group” interactions nor significant “group” effects were seen for lorazepam and zopiclone (P values between 0.541 and 0.657). Thus, the use of concomitant medication (lorazepam, zopiclone) was comparable in both treatment groups (Table II). Moreover, no significant effects were found in repeated-measures ANOVA with regard to mirtazapine levels (“time”: $F = 0.228$; $df = 2.455$, 81.017; $P = 0.839$; “time” × “group”: $F = 0.656$; $df = 2.455$, 81.017; $P = 0.552$; “group”: $F = 0.762$; $df = 1$, 33; $P = 0.389$), suggesting that the mirtazapine concentrations were stable during the 4-week treatment period and did not differ significantly between both treatment groups (Table II).

Side effects, safety and tolerability

ANOVA for repeated measurements revealed a significant “time” effect for both weight ($F = 14.928$; $df = 1.905$, 72.390; $P < 0.001$) and BMI ($F = 15.462$; $df = 1.962$, 74.564; $P < 0.001$), indicating a significant increase in weight and body mass index (BMI) in the overall patient group during the treatment period. Patients treated with mirtazapine monotherapy had a weight gain from 68.82 ± 15.90 to 70.92 ± 16.67 kg and an increase in BMI from 24.29 ± 4.05 to 25.02 ± 4.19 during the 4-week treatment period. Four-week combination therapy with mirtazapine and aripiprazole also caused an increase in both weight (78.70 ± 21.32 to 79.61 ± 21.11 kg) and BMI (26.99 ± 6.05 to 27.30 ± 5.87), but the changes in weight and BMI were somewhat smaller. There was a statistical trend for a relevant “time” × “group” interaction effect regarding weight ($F = 2.797$; $df = 1.905$, 72.390; $P = 0.070$) and a significant “time” × “group” interaction effect with respect to BMI ($F = 3.162$; $df = 1.962$, 74.564;

$P = 0.049$). No significant “group” effects could be shown: (a) weight: $F = 2.290$; $df = 1$, 38; $P = 0.138$; (b) BMI: $F = 2.190$; $df = 1$, 38; $P = 0.147$). Nevertheless, the trend for or the significance of interaction effects suggested a relevant impact of the kind of treatment on the amount of weight gain or increase in BMI, being lower when aripiprazole was given additionally.

There was little evidence for extrapyramidal side effects during the 4-week study period. Clinically relevant symptoms of parkinsonism such as rigidity, tremor, increased salivation or pathological glabella tap reaction did not occur in any of the patients, neither in the mirtazapine group nor in the combination therapy group. Only one patient receiving mirtazapine and aripiprazole reported a moderate akathisia-like agitation during the first 2 weeks of treatment. However, there were also two patients treated with mirtazapine monotherapy who gave an account of mild to moderate akathisia during the first week, which might be due to depression-induced agitation and not an extrapyramidal side effect. In one patient receiving combination therapy a transient mild singultus was observed. Moreover, one patient out of the combination therapy group reported on slight deterioration of sleep difficulties. No changes in vital parameters (blood pressure, heart rate) or other side effects of clinical relevance and no clinically significant laboratory abnormalities occurred during the 4-week trial, except for one female patient who showed elevated liver enzymes during the first week of mirtazapine monotherapy and was not subjected to further analysis (see above). In addition, ECG recordings did not display any relevant abnormalities at the end of the study, in particular no significant prolongation of the QTc interval.

When analysing the Simpson–Angus Scale (SAS), patients out of the combination therapy group tended to have even less extrapyramidal side effects

Table II. Dosages of lorazepam and zopiclone and levels of mirtazapine and aripiprazole in depressed patients treated with monotherapy (mirtazapine 45 mg/day) or combination therapy (mirtazapine 45 mg/day and aripiprazole 15 mg/day) over 4 weeks. Data represent mean ± SD (standard deviation).

	Monotherapy lorazepam (mg)	Combination therapy	Monotherapy zopiclone (mg)	Combination therapy
Week 1	1.34 ± 1.21	1.02 ± 1.07	4.88 ± 3.67	4.13 ± 3.63
Week 2	1.02 ± 0.91	0.88 ± 0.89	4.31 ± 3.71	3.56 ± 3.54
Week 3	0.79 ± 0.97	0.74 ± 0.83	3.56 ± 3.75	3.38 ± 3.63
Week 4	0.69 ± 0.98	0.63 ± 0.89	3.19 ± 3.50	3.00 ± 3.35
	Monotherapy mirtazapine (ng/ml)	Combination therapy aripiprazole (ng/ml)	Monotherapy	Combination therapy
Week 1	69.11 ± 22.46	57.82 ± 20.05	0.00 ± 0.00	58.40 ± 30.27
Week 2	68.67 ± 22.81	60.71 ± 31.64	0.00 ± 0.00	64.40 ± 28.11
Week 3	66.83 ± 18.32	60.29 ± 32.45	0.00 ± 0.00	88.80 ± 57.00
Week 4	67.00 ± 22.57	64.47 ± 37.23	0.00 ± 0.00	86.60 ± 50.11

during the first 2 weeks of treatment (Figure 1B). Repeated-measures ANOVA of SAS sum scores did not reveal any significant effects (a) "time": $F=0.837$; $df=2.457, 93.361$; $P=0.457$; (b) "time" \times "group": $F=1.184$; $df=2.457, 93.361$; (c) "group": $F=0.167$; $df=1, 38$; $P=0.685$). Regarding the Barnes Akathisia Scale (BAS), the overall sum scores were very low in both treatment groups. There was a slight and transient increase of akathisia-like symptoms in the combination therapy group during the first 2 weeks of treatment (Figure 1C). Repeated-measures ANOVA of BAS sum scores did not demonstrate any significant effects either (a) "time": $F=0.783$; $df=2.247, 85.399$; $P=0.474$; (b) "time" \times "group": $F=0.621$; $df=2.247, 85.399$; $P=0.558$; (c) "group": $F=0.475$; $df=1, 38$; $P=0.495$).

Taken together, both mirtazapine treatment and combined therapy with mirtazapine and aripiprazole were well tolerated.

Discussion

This open-label trial is the first parallel group study investigating the efficacy and tolerability of additional treatment with aripiprazole in depressed patients. The response rates (monotherapy: 55.0%; combination therapy: 60.0%) and the remission rates (monotherapy: 20.0%; combination therapy: 25.0%) after 4 weeks of treatment are in the range which can be expected in clinical trials of similar design (Baghai et al. 2006), in particular if the fact is considered that 15 out of 40 patients included in the study suffered from treatment-resistant depression (TRD) (Fava and Davidson 1996). Mirtazapine monotherapy and combination therapy with mirtazapine and aripiprazole did not differ significantly with respect to clinical efficacy at the endpoint of the 4-week treatment period. Moreover, when analysing the overall patient group, survival analysis of time until response did not reveal any differences between the monotherapy group and the combination therapy group. However, in a separate analysis for patients with and without TRD, certain differences in the time course of onset of action became obvious: whereas in the monotherapy group patients with TRD displayed a significantly delayed onset of antidepressant action when compared with patients without TRD, such a difference could not be seen in the combination therapy group, suggesting that additional treatment with aripiprazole caused an earlier treatment response particularly in patients suffering from TRD. Since the speed of antidepressant response is an important variable, especially when patients are experiencing suicidal ideations (Kennedy and Lam 2003), this finding appears to be

of clinical relevance. Although our investigation is limited by the fact that only 15 out of 40 patients suffered from TRD and precaution in interpreting the results is therefore required, our data suggest that in particular patients with TRD may benefit from additional treatment with aripiprazole, which is in line with former open-label studies and case series reporting clinical usefulness of aripiprazole augmentation in TRD (Barbee et al. 2004; Hellerstein 2004; Papakostas et al. 2005; Simon and Nemeroff 2005; Worthington et al. 2005). Consistent with the results from trials investigating other atypical antipsychotics (Ostroff and Nelson 1999; Papakostas et al. 2004; Shelton et al. 2001), the addition of aripiprazole to serotonergic antidepressant treatment options such as SSRIs or mirtazapine obviously results in a more rapid improvement of depressive symptoms in TRD.

A further important result of our study is the finding that this combination therapy was very well tolerated in depressed patients. First, the weight gain which was demonstrated for mirtazapine in several clinical trials (Fawcett and Barkin 1998) was less pronounced in our study if aripiprazole was administered additionally. The increase in body weight in the monotherapy group of our study after 4 weeks of treatment (2.1 kg) was comparable to that reported in a previous study finding that 4-week therapy with mirtazapine induces a weight gain of 2.4 kg (Kraus et al. 2002). The smaller amount in weight gain after 4 weeks in the combination therapy group of our study (0.9 kg) is in line with former short-term trials, suggesting that aripiprazole only induces small increases in body weight (0.7–1.2 kg) in schizophrenic patients (Kane et al. 2002; Marder et al. 2003; Potkin et al. 2003) and no weight gain at all in bipolar patients (Keck et al. 2003). However, when comparing weight gain and BMI in both treatment groups, it has to be mentioned that the average weight and BMI at baseline were somewhat higher in the combination therapy group than in the monotherapy group (Table I) which possibly had an impact on the weight changes during the treatment period.

Second, no clinically relevant changes in heart rate or mean arterial blood pressure occurred and no significant changes or abnormalities in the ECG, in particular no prolongation of the QTc interval, were found after 4-week additional treatment with aripiprazole. Thus, aripiprazole seems also to be safe and well tolerable with regard to vital signs and ECG parameters as it has been found in former clinical trials (Bowles and Levin 2003; Marder et al. 2003; Pigott et al. 2003).

A third important issue concerning the safety and tolerability profile of aripiprazole in our study is related to the absence of extrapyramidal side effects

and the very low rate of akathisia in depressed patients treated with both mirtazapine and aripiprazole. Neither clinical examinations of the patients nor the application of rating scales (SAS, BAS) revealed any significant impact of aripiprazole on the extrapyramidal motor system as compared to mirtazapine monotherapy. Aripiprazole is known not to induce extrapyramidal symptoms even with striatal D₂ receptor occupancy values above 90% at higher dosages (Yokoi et al. 2002), suggesting that theories claiming the occurrence of extrapyramidal side effects with D₂ receptor occupancy higher than around 80% in antipsychotics (Farde et al. 1992) are not applicable for partial D₂ receptor agonists such as aripiprazole (Grunder et al. 2003). However, aripiprazole may cause akathisia in patients suffering from different psychiatric diagnoses. The BAS score was significantly increased after 15 mg aripiprazole monotherapy in schizophrenic patients as compared to placebo, albeit not any dosage of aripiprazole caused akathisia and a dose-dependent relationship could not be established (Marder et al. 2003). In previous studies investigating combined treatment with aripiprazole and SSRIs in depressed patients, the occurrence of akathisia also involved clinically relevant problems: about one half of the depressed patients experienced akathisia or mild extrapyramidal side effects when moving the dosage from 5 to 10 mg per day in one study (Adson et al. 2005); in another study 16.7% of the depressed patients complained about restlessness or akathisia which forced in part to premature discontinuation of the participation (Papakostas et al. 2005); and three out of 15 depressed patients discontinued prematurely because of aripiprazole-induced akathisia in the trial of Simon and Nemeroff (2005). It is even hypothesized that patients suffering from depression (Adson et al. 2005) or from bipolar mania (Keck et al. 2003) may be more sensitive to akathisia during aripiprazole treatment than schizophrenic patients. However, in contrast to combined treatment with SSRIs and aripiprazole, combination therapy with mirtazapine and aripiprazole is apparently not associated with a higher risk for akathisia, as it is demonstrated in our study. This observation is confirmed by case reports (Poyurovsky and Weizman 2001; Ranjan et al. 2006) and double-blind placebo-controlled studies (Poyurovsky et al. 2003; Poyurovsky et al. 2006), suggesting good efficacy of concomitant mirtazapine administration in antipsychotics-induced akathisia.

In our study, additive administration of aripiprazole had no impact on mirtazapine blood levels. This is in line with the Physicians Desk Reference (PDR; http://www.pdrhealth.com/drug_info/index.html) indicating that neither aripiprazole nor mirtazapine are

likely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 isoenzymes.

Taken together, in this 4-week parallel-group trial mirtazapine monotherapy and combined treatment with mirtazapine and aripiprazole were equally effective in depressed patients without psychotic symptoms, as assessed at the endpoint of the study period. Due to the open-label design, the small sample size and the lacking placebo condition this comparison of clinical efficacy is very preliminary and has to be further investigated in larger controlled trials. Interestingly, additional administration of aripiprazole appeared to accelerate the onset of antidepressant action in patients suffering from treatment-resistant depression. Combined therapy with mirtazapine and aripiprazole was safe and very well tolerated. Additive use of aripiprazole tended to reduce the mirtazapine-induced weight gain and significantly diminished the increase in BMI during mirtazapine treatment. On the other hand, mirtazapine apparently had favourable effects on akathisia which is known to be a relevant side effect during aripiprazole therapy, especially in affective disorders. Since the conclusions which can be drawn from the present trial are limited due to the open-label design, double-blind controlled studies are needed to further explore the efficacy and safety of aripiprazole in depressed patients.

Acknowledgements/Statement of interest

The study was done in the framework of the doctoral thesis of Ms Susanne Hecht which will be submitted to the Faculty of Medicine, Ludwig-Maximilian-University of Munich. The trial was an investigator-initiated study and was performed by the exclusive responsibility of the authors. The study was supported by an unrestricted grant of the Bristol-Myers Squibb pharmaceutical company which did not have any impact on performing the study and evaluating or interpreting the data. Dr. Rupprecht has served as consultant to or on the advisory boards of the pharmaceutical companies Novartis, Sepracor, Sanofi-Synthelabo. With regard to all other authors, there are no conflicts of interest to be disclosed.

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CASE REPORT

Clinical improvement in a case of frontotemporal dementia under aripiprazole treatment corresponds to partial recovery of disturbed frontal glucose metabolism

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Abstract

Frontotemporal dementia (FTD) is increasingly recognized as an important type of degenerative dementia but satisfactory pharmacological treatment has not yet been established. We examined the clinical effects of aripiprazole, a new antipsychotic with partial agonistic properties at serotonin 5-HT_{1A} and dopamine D₂ receptors, in parallel with cortical glucose metabolism changes. We conducted a follow-up investigation of clinical status and ¹⁸F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) in a 73-year-old male patient with FTD over a 13-month period. Under conventional drug treatment during the first 12 months a marked increase in dementia symptoms was observed. Frontal lobe glucose metabolism clearly decreased during this time period. Under consecutive treatment with aripiprazole a significant and stable improvement of clinical symptoms could be registered, while disturbed frontal glucose metabolism increased significantly. According to this case experience, further investigations should be undertaken to ascertain whether aripiprazole or other atypical antipsychotics with properties to improve impaired dopaminergic transmission in frontal brain regions could qualify for therapy of FTD.

Key words: Frontotemporal dementia, FTD, FDG-PET, aripiprazole, treatment

Introduction

Frontotemporal dementia (FTD) is increasingly recognized as an important type of degenerative dementia (Neary et al. 1998, 2005). As degeneration of serotonergic neurons in frontal lobes seems to be involved in the pathophysiology of FTD (Sparks and Markesbery 1991; Procter et al. 1999), serotonergic agents have been primarily proposed for treatment. Studies with serotonin reuptake inhibitors revealed inconsistent findings (Swartz et al. 1997), but trazodone significantly reduced behavioural disturbances in FTD patients without effects on cognition (Lebert et al. 2004). In animal studies, trazodone increased extracellular 5-HT levels in the frontal cortex mainly due to 5-HT_{1A} receptor agonistic effects (Mizoguchi et al. 2002), leading to increased dopamine release (Ago et al. 2003). Dopaminergic pathways seem also primarily affected in FTD (Rinne et al. 2002), and beneficial effects of methylphenidate in single patients with FTD (Goforth

et al. 2004) were attributed to improved dopamine availability (Volkow et al. 2000) associated with enhanced attention, motivation, and working memory (Volkow et al. 2004).

Therefore, combined dopaminergic and 5-HT_{1A}-agonistic effects of the atypical antipsychotic aripiprazole (Jordan et al. 2004) could be beneficial in the treatment of FTD.

The case

The 73-year-old male patient was admitted to a gerontopsychiatric division after a 3–4-year history of cognitive decline and behavioural change dominated by progressive apathy, loss of motivation, reduction of speech, and emotional indifference. Psychiatric examination yielded severely disturbed executive functioning and attention, and affective indifference. Memory function was impaired due to motivational deficits, whereas orientation was preserved. The CGI-2 and the negative syndrome

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subscale of the PANSS (Kay et al. 1987) were used to quantify the predominant symptoms and indicated a severe negative syndrome.

There was no family history of neurodegenerative diseases. Cerebrospinal fluid (CSF) total tau protein level was elevated, other laboratory findings including thyroid hormones, *Treponema pallidum* and *Borrelia* antibodies, vitamin B12 and folic acid, as well as CSF levels of amyloid A β_{1-42} and tau protein phosphorylated at threonine 181 were regular. Cranial MRI scan showed a frontally pronounced cortical atrophy. Electroencephalogram (EEG) findings were normal (11/s alpha rhythm). FDG-PET showed significant frontal glucose hypometabolism pronounced at the right side (Figure 1, scan 1).

Clinical diagnosis of FTD was made according to consensus guidelines (Neary et al. 1998) and was supported by structural imaging findings, FDG-PET findings, and the CSF biomarker profile. Beside the pronounced and progressive negative syndrome, no psychotic features were present; additionally, the patient had no history of schizophrenia or other psychotic disorders. Although the onset of FTD is usually earlier than in the present case (between 45 and 65 years) (Neary et al. 2005), FTD can be found also late in life (Gislason et al. 2003). Treatment with sertraline 50 mg/day was initiated.

Follow-up

Despite increasing the sertraline dose to 100 mg/day and additional treatment with the NMDA-receptor antagonist memantine up to 10 mg/day, the clinical state deteriorated continuously over 1 year. Particularly, motivation and activity worsened; the patient got used to lying in bed most of the day. Speech was reduced to short sentences on demand, and the patient became incontinent. Emotionally, he seemed to be fully unconcerned about his growing helplessness and the increasing distress of his wife. The Mini Mental State Examination (MMSE) score was diminished from initially 26 points to 22 points at follow-up, and the PANSS negative symptom score also indicated deterioration (Table I).

FDG-PET control after 13 months showed progressive hypometabolism clearly pronounced in the frontal lobes (Figure 1, scan 2). At this stage, aripiprazole treatment was initiated at 10 mg/day. After 5–7 days a significant improvement of the severe apathy syndrome could be observed. The patient wanted to go out for a walk, and started to talk about everyday life. He began to worry about his wife. After 5 weeks with stable behavioural improvement, the MMSE score increased from 22 to 24 points, and the PANSS negative symptom scale indicated a substantial clinical improvement of, however, still prevailing negative symptoms

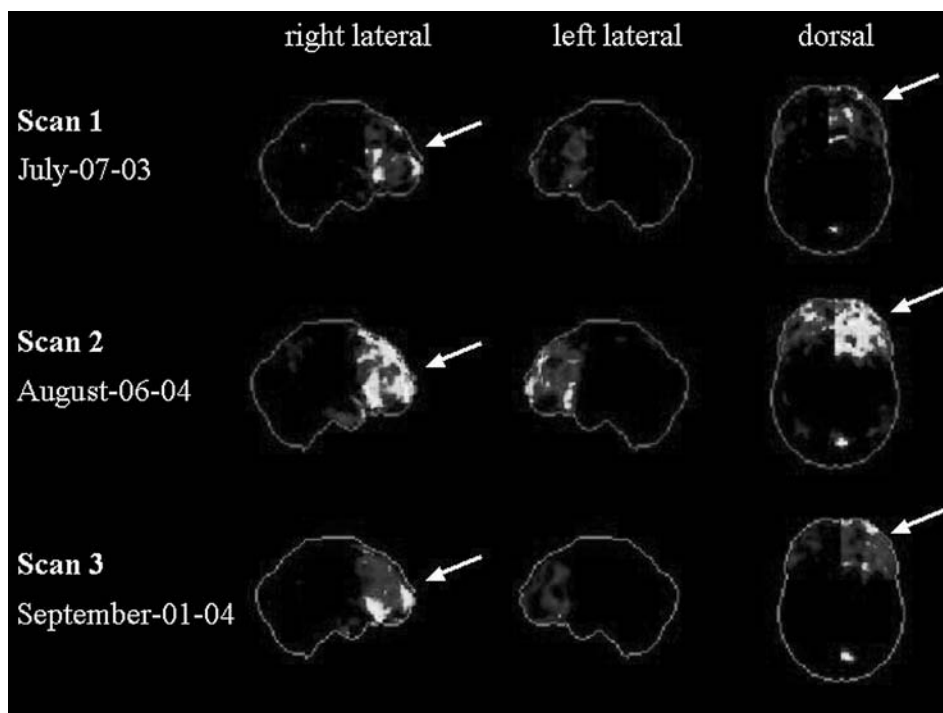


Figure 1. ^{18}F -FDG-PET findings: the comparison with the normal database showed marked decrease of cerebral frontal glucose metabolism pronounced on the right side (see arrows) over the 13-month period (scans 1 and 2). Under aripiprazole treatment, partial restitution of disturbed frontal glucose metabolism could be observed (scans 2 and 3).

Table I. Clinical characteristics at baseline and follow-up assessment.

	Baseline	+13 months	+5 weeks
FDG-PET	Figure 1, scan 1	Figure 1, scan 2	Figure 1, scan 3
PANSS-NEG	22	29	25
MMSE	26	22	24
CGI-2 change clinician	0 (n.a.)	5 (moderately worse)	2 (much better)
CGI-2 change caregiver	0 (n.a.)	6 (much worse)	2 (much better)
Pharmacological treatment	–	Sertraline 50–100 mg after 6 months: +Memantine 5–10 mg	Aripiprazole 10 mg

n.a., not accessible; PANSS-NEG, Positive and Negative Syndrome Scale, negative syndrome subscore (seven items, scored 0–6) (16); MMSE, Mini Mental State Examination (max. 30 points) scores <25 indicate dementia; CGI-2, Clinical Global Impressions, global clinical improvement rating (single item, score 1–7); the CGI score was independently assessed by a clinician and the patient's caregiver.

(Table I). Quantitative analysis yielded a considerable increase in glucose metabolism in the bilateral prefrontal cortex (right: +27.9%; left: +27.0%) and premotor cortex (right: +32.6%; left: +23.9%) as well as in the anterior temporal cortex (right: +11.0%; left: +42.5%) in parallel to clinical improvement after aripiprazole treatment (Figure 1, scans 2–3).

PET data acquisition and analysis

PET scans (ECAT Exact PET Scanner; Siemens/CTI, Knoxville, USA) under standard resting conditions were started 30 min after intravenous injection of 160–180 MBq ¹⁸F-fluorine-deoxyglucose (18-FDG) and continued for 15 min in a three-dimensional acquisition with an axial 16.2-cm field of view. Attenuation correction was done by computerized threshold limit routine to define an isodensity contour for maximum cerebral activity/pixel. A total of 47 transverse slices (slice thickness 3.375 mm) were reconstructed (4-mm Hamming filter; transaxial full-width-at-half-maximum 6.0 mm). Automated analysis of PET image data generated standardized three-dimensional stereotactic surface projections of individual datasets followed by voxel-to-voxel comparison with an age-matched normal data base (25 volunteers, age range 53–76 years) resulting in parametric *z*-score images (Minoshima et al. 1995). Changes of regional cerebral glucose metabolism after aripiprazole therapy were quantified by additional ROI-based analyses of standardized anatomical regions (Drzezga et al. 1999). For data normalization the sensorimotor cortex served as reference region (Santens et al. 2001; Fellgiebel et al. 2003).

Discussion

This prospective observation demonstrates clinical improvement of a patient with FTD related to partial restitution of impaired frontal glucose metabolism under aripiprazole treatment. The

improvement of clinical symptoms was stable over an observation period of more than 2 months. The patient's syndrome consisted mainly of severe apathy, speech reduction, and emotional withdrawal, whereas other behavioural characteristics of FTD were not present. Thus, the clinical syndrome of the patient who had no history of a psychotic disorder was phenotypically similar to the negative symptomatology observed in chronic schizophrenia which has been related to diminished dopaminergic neurotransmission in prefrontal and frontal brain regions (Knable and Weinberger 1997). Due to partial agonistic properties at D₂ and 5-HT_{1A} receptors in combination with 5-HT₂ receptor blockade, aripiprazole at low doses might enhance dopamine release in the hippocampus and in the medial prefrontal cortex, but not in the nucleus accumbens (Li et al. 2004). No substantial effect of aripiprazole on acetylcholine release has been reported (Li et al. 2004) making cholinergic effects unlikely to be responsible for the present findings. Additionally, enhanced serotonin availability by sertraline and glutamatergic receptor modulation by memantine were not successful in the present case. Further investigations should ascertain whether drugs like aripiprazole with properties to enhance frontal dopamine turnover could qualify for therapy of negative symptoms in FTD.

Particularly in older patients with dementia and vascular risk factors, the safety of antipsychotics has recently been questioned (Herrmann and Lanctot 2005). Aripiprazole is not approved for patients with dementia, and most recently, manufacturer's information (Otsuka Pharmaceuticals 2005) raises concern whether aripiprazole treatment might be associated with cerebrovascular events in patients with psychosis and Alzheimer's dementia. The patient presented here had no vascular risk factors, and no adverse event was observed under aripiprazole treatment. However, safety considerations, e.g., low doses, avoiding polypharmacy, and frequent

monitoring, are undoubtedly warranted when treating FTD patients with new drugs.

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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CASE REPORT

Autistic disorder and 22q11.2 duplication

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Abstract

Although several reports have described the co-occurrence of autism in subjects with chromosome 22 abnormalities including trisomy 22, translocation 20/22, 22q11.2 deletion, ring chromosome 22, and 22q13.3 deletion, there is no report with 22q11.2 duplication. We report a 9-year-old girl, referred to our department for her behavioural problems and language delay. She was diagnosed with autistic disorder according to DSM-IV criteria. Because of her dysmorphic characteristics comprising narrow face, narrow forehead, mandibular prognathism, synophrys, and operated cleft palate and cardiac problems, she had gone under cytogenetic analysis. Although she was ascertained as suspected velocardiofacial syndrome (VCFS), the duplication of 22q11.2 was detected by interphase fluorescence *in situ* hybridization. Previous reports on the psychiatric aspects of 22q11.2 duplication have shown the existence of hyperactivity, learning disability, speech problems, and aggressive behaviours but not autism. Moreover, the lack of reports of co-occurrence of autism and 22q11.2 duplication may be related to paucity as a result of technical problems.

Key words: 22q11.2 duplication, autistic disorder, chromosome 22, interphase FISH, velocardiofacial syndrome

Introduction

Genetic factors have been shown to play an important role in the aetiology of autism spectrum disorder, but to date no clear mode of inheritance has been identified (Vorstman et al. 2006). Association between structural or numerical abnormalities of chromosome 22 and autism have been reported in several case reports, these include trisomy 22 (Turner and Jennings 1962), translocation 20/22 (Carratala et al. 1998), 22q11.2 deletion (Kozma 1998), 22q13.3 deletion (Prasad et al. 2000), ring chromosome 22 (MacLean et al. 2000), but not 22q11.2 duplication.

Chromosome 22q11.2 has long been implicated in genomic diseases such as 22q11.2 deletion syndrome (DiGeorge/velocardiofacial syndrome), der (22) and cat-eye syndrome, which are associated with either decreased or increased gene dosage. There is considerable overlap in the clinical presentation between these conditions, although each has a recognizably distinct phenotype (Edelmann et al. 1999). Recently, there have been reports on patients with duplication of 22q11.2, establishing the complementary genomic disorder of the 22q11.2

deletion syndrome (Edelmann et al. 1999; Ensenuer et al. 2003; Hased et al. 2004a; Beiraghi et al. 2005; Lamb et al. 2005; Portnoi et al. 2005; Somerville et al. 2005; Sparkes et al. 2005; Yobb et al. 2005). It was shown that the phenotype of these patients is extremely diverse, ranging from mild learning disability to severe congenital malformations or some overlapping features with 22q11.2 deletion syndrome, and it appears to represent a distinct syndrome (Edelmann et al. 1999; Ensenuer et al. 2003). The majority of these patients had psychiatric problems such as hyperactivity, learning disability, speech problems, and aggressive behaviours. However, autistic disorder was not reported. Here, we report a girl with autistic disorder and duplication of 22q11.2. To our knowledge, this is the first case report on autistic disorder and 22q11 duplication.

Case

Identifying data

The patient is a 9-year-old girl who is the third child of a 34-year-old mother and 44-year-old father. Her

parents are second cousins. She was referred to our clinic by her parents because of her behavioural problems and language delay.

Psychiatric evaluation

Her psychiatric evaluation revealed deficits in socio-emotional areas, such as lack of eye contact, joint attention, impairment in social response, and severe impairment in imitative plays and abilities. According to her parents, she was unable to interact with her peers, and generally preferred to stay alone. She had no pretend play, no interest in her toys, and was not able to sustain reciprocal interaction. She had only five meaningful words, and she had limitation in understanding comment. She had stereotypical behaviours such as licking her lips, and shaking her hands. Her adaptive function level was assessed using the Turkish version of the Vineland Adaptive Function Scale (test-retest reliability for all domains ranged from 0.91 to 0.98, inter-rater reliability for all domains ranged from 0.97 to 0.99, Cronbach's α coefficient for all domains: 0.95–0.97) (Alpas 2002). Her age equivalent on communication was 1 year, 2 months; on daily life skills: 3 years; socialization: 1 year, 3 months; and motor domains: 3 years, 11 months. The Turkish version of the Childhood Autism Rating Scale (CARS) (Cronbach's $\alpha = 0.86$, item-total correlation: 0.60–0.91; discriminant validity: $p < 0.005$ for 11 items and $p < 0.05$ for three items) (Sucuglu et al. 1996) and the Turkish version of the Autism Behaviour Checklist (ABC) (Cronbach's $\alpha = 0.96$, and Spearman-Brown two half-split coefficient: 0.96) (Gurkan and Sutcu 2004) were used to evaluate the severity of her autistic symptoms. Her total score in CARS was 40 (indicating severe autism) and in ABC was 86. She was diagnosed with autistic disorder according to DSM-IV (American Psychiatric Association, 1994).

Developmental history

She was born at term after an uneventful pregnancy. Her birth weight was 2800 g and she was 50 cm long. She had feeding problems due to a cleft plate, and had undergone surgery at 5 years old. She had a history of febrile convulsion at the age of 4.

Her gross motor milestones were severely delayed; she sat at 24 months, and first walked at 36 months. Significant speech delay was also noted; she started using single words at the age of 6. Her impairment in the socio-emotional area, including lack of response to calling her name, lack of eye contact and imitative abilities, was noticed from early childhood.

Physical examination

On admission, her weight was 18.3 kg (25 th percentile), her height 114 cm (50–75 th percentile), and her head circumference was 51 cm (25–50 th percentile). She had a facial dysmorphism, including narrow face and narrow forehead, mandibular prognathism, synophrys and operated cleft palate. In addition, she had low medial arcus in her feet, and positional abnormalities in her toes. alternant exotropia and hypermetropia were detected in her ophthalmological examination. Cardiovascular examination revealed mild mitral insufficiency and mitral valve prolapsus. Audiometry, extensive metabolic testing, thyroid function tests, cranial computed tomography, brain magnetic resonance imagery, electroencephalography, and abdominal ultrasonound were normal.

On clinical grounds, a diagnosis of velocardiofacial syndrome (VCFS) was considered and she was referred for genetic consulting. G-banded chromosome analysis showed a normal female karyotype. Initial fluorescence *in situ* hybridization (FISH) analysis of metaphase cells showed two areas of fluorescence. Further analysis of interphase cells revealed duplication on one chromosome, reflecting increased gene dosage in the 22q11.2 region. The patient had the following karyotype: 46, XX, ish dup (22)(q11.2–11.2) (D22S75 ++, N85A3+). Genetic investigation of her family, showed the same duplication in her father.

Family history

Her father had synophry and narrow face. His psychiatric evaluation showed no major psychopathology in his mood, affect, thought, and perception. However, he was defined as an introvert man, with some obsessive traits according to his wife. He has his own small business, and has no difficulty in managing his life. He had a history of learning disability in primary school and had to leave school after primary school.

The mother had a history of academic failure in primary school, and she could not continue her education after the first 2 years of school. She was an illiterate housewife with a reasonable level of social abilities. Her brothers were physically healthy, with average academic achievement, and some minor limitations in social interactions.

Her maternal great uncle was diagnosed with autistic disorder, and her maternal cousin (male) was mentally retarded, and her two paternal cousins (both female) had epileptic seizures.

Discussion

We describe a girl with autistic disorder, who was ascertained as a suspected VCFS case because of operated cleft palate, facial dysmorphism, cardiac problems, and cognitive deficits. Although a normal karyotype was found on routine chromosome analysis, duplication of the 22q11.2 region became evident when using interphase FISH. To the best of our knowledge, except for a case reported by Hased et al. (2004b) on features of Asperger syndrome in a case with 22q11.2 duplication, this paper is the first report on co-occurrence of autistic disorder in this group. Here, we discuss the diagnosis of autism, the clinical phenotype, and the factors that influenced the phenotypic outcome in this subject.

The first point that needs to be discussed is the diagnosis of autistic disorder in this case. Since diagnosis of autistic disorder is made based on behavioural abnormalities, it is not easy to define it in cases with several medical problems and severe mental retardation. Because of her mental retardation it was not easy to differentiate between autistic disorder and mental retardation. However, at the time of evaluation, she showed the typical triad of autism, consisting of deficits in socialisation, communication and play. Based on the parents' statements, her social-communicative limitation and stereotypical behaviours have been present since early childhood, and her limitations in these areas is more pronounced than her cognitive deficits. Therefore, she received a diagnosis of autistic disorder according to DSM-IV criteria.

The second point is the comparison of her phenotype with previous cases reported in the literature. According to our knowledge, after the first case report of '22q11.2 duplication' by Edelman et al. (1999), only 30 cases with this condition have been reported. The phenotype of these patients is reported to be variable, ranging from normal to multiple defects including cleft palate, urogenital abnormalities, hearts defects, hearing loss, growth deficiency, global developmental delay, cognitive-behavioural problems, and psychiatric abnormalities, including hyperactivity, anxiety and aggressive behaviours. Comparing the phenotype of our patient with previous reports on microduplication 22q11.2 syndrome shows that, although she has some similarities with previously reported cases, such as narrow face, synophrys, cleft palate, foot abnormality, cardiac problems, and developmental delay, she additionally suffers from autistic disorder.

The presence of same duplication with a different outcome in her father is an important point that needs further discussion. Her father had narrow face, synophrys, and introvert personality with history of

learning disability. However, he had his own business and could manage his family and his life. The difference between her clinical phenotype with her father is consistent with that reported earlier. Marked inter- and intrafamilial variability was reported in this group by Ensenauer et al. (2003). They stated that different degrees of mental impairment may be present within the same family, despite the same duplication size in the family (Ensenauer et al. 2003).

Another important issue is the role of factors that lead to co-occurrence of 22q11.2 duplication and autism in this case. The presence of positive family history of autism and mental retardation in her maternal relatives, epilepsy and mental retardation in her paternal relatives may have contributed to her clinical outcome. Therefore, the influence of positive family history along with chromosomal abnormality could be major factors leading to autism in this subject.

Considering the relationship between chromosome 22 and autism, there are increasing numbers of reports on autistic spectrum disorders in subjects with 22q11.2 deletion (Niklasson et al. 2002; Fine et al. 2005). The lack of reports on autism and 22q11.2 duplication could be related to the paucity due to technical difficulty.

Although the present paper has some limitations, such as lack of assessment with structured interview forms (due to unavailability in Turkish), it may add new information to the growing literature on complementary duplication/deletion syndromes that are proposed to cause disease via increased or decreased genetic dosage.

In conclusion, increased awareness of the phenotype associated with 22q11.2 duplication may aid in the molecular genetic analysis of this chromosomal abnormality and clarify its relationship with autism. Furthermore, because of the tendency for learning disability and mental retardation in cases with 22q11.2 duplication, we recommend that future research should include assessment of their social skills.

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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LETTER TO THE EDITOR

Comments on the report of neuroleptic malignant syndrome induced by ziprasidone

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Dear Editor,

We read with interest the report by Ozen et al. (2007) on neuroleptic malignant syndrome (NMS) induced by ziprasidone recently published in your journal. Though articles on this condition are important and should be encouraged, this article gives rise to a few comments.

The report represents the patient with schizophrenia who was hospitalised because of psychotic symptoms. He developed NMS the second day after treatment with ziprasidone. After withdrawal of NMS symptoms, by the 11th day of admission, the patient was discharged. It is not clear whether the patient was psychotic or not during discharge. Olanzapine (5 mg/day) was administered in the follow-up period, but when did the follow-up period begin and how long was that period? The authors offer information that can be understood in opposite ways. One may understand that olanzapine was administered on the same day that the patient was discharged, and that the authors have no proof that the patient took the single dose of medication. Another possibility is that the authors have followed the patient for a certain period of time, and that they can confirm that olanzapine at a dose of 5 mg/day was not just the cause of another NMS, but that the patient's psychotic process was well controlled. But what actually happened? The authors recommend caution when starting to use an atypical antipsychotic. Thus, is it possible that the patient got his first dose of olanzapine as an out-patient, just 11 days after he developed NMS due only to the one pill of ziprasidone?

Lethal catatonia cannot be excluded because of diaphoresis, muscle rigidity, elevated CK, or leuko-

cytosis. On the contrary, according to some authors NMS is a neurotoxic state which has features that are indistinguishable from those of malignant (or lethal) catatonia (Fink and Taylor 2001). The differentiation between lethal catatonia and NMS may be moot, and it is reasonable to consider that NMS is a neuroleptic-induced form of lethal catatonia (Otani et al. 2006). Thus, it is more than questionable whether NMS and lethal catatonia are distinct entities.

Furthermore, the authors use the protocol by which the combination of diazepam, biperiden and fluid replacement: "... is commonly used and is still the best known effective way of coping with such a highly lethal state as NMS in a short time period". Although reports on the beneficial effect of benzodiazepines exist, some authors suggest that the difference between lethal catatonia and NMS exists in the response to treatment with benzodiazepines, which have proven efficacy in lethal catatonia, but not in NMS (Ananth et al. 2004a). On the other hand, it is worth mentioning that the syndrome (sometimes differently called) has been reported during withdrawal of some medications, such as benzodiazepines and anticholinergics used here. In our opinion it is very rational to use these medications in the treatment, but we have the impression that some other drugs, such as dantrolene or bromocriptine, are more often mentioned in the literature as options for the treatment of this condition. Anyhow, firm guidelines do not exist (Otani et al. 2006). Accordingly, it would be helpful if the authors provided information on doses and duration of treatment.

It is reported that NMS usually develops within the first 4 weeks of starting antipsychotic medication, most characteristically in 24–72 h after the administration of a neuroleptic agent or a change in dosage (usually an increase), sometimes after a single dose, but it can occur in patients who have been stable on the medications for months or years (Hall et al. 2006). Yet, the mean number of days from the initiation of treatment to the onset of NMS, similarly as for mean number of days for recovery, could be very different for different atypical antipsychotics (Ananth et al. 2004b). Thus, the information about early onset of NMS due to ziprasidone treatment is important (Ozen et al. 2007).

Finally, there are not just “some cases” of NMS due to atypical antipsychotics, but dozens at least (Ananth et al. 2004b).

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LETTER TO THE EDITOR

Neuroleptic malignant syndrome induced by ziprasidone on the second day of treatment: A case report

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Dear Editor,

This article is in reply to “Comments on the report of neuroleptic malignant syndrome induced by ziprasidone” by Branimir Margetić and Branka Aukst-Margetić (Margetić and Aukst-Margetić 2007), and we answer their queries on our case report.

We took the patient under custody with the help of our service crew to prevent harm to ourselves or the patient, and to prevent a suicide attempt. We carried out regular visits. Administration of only a single dose of ziprasidone was documented. We noted that no other psychotropic drug was used. It was carefully observed that the patient had not taken any other antipsychotic drugs, including ziprasidone.

On examination during the period after discharge, the patient still had psychotic signs, so we decided to prescribe another atypical antipsychotic for maintenance. Olanzapine was administered on the 10th day after discharge (the 20th day from application). We followed-up the patient 3 months after discharge on olanzapine treatment. In the follow-up, the patient was called for visits twice a week, accompanied by family members.

We documented the illness history with the help of family members. There was no mood component in the course of the illness. In fact, many lethal catatonic states include a mood component; most cases give a history of depression with psychotic features or bipolar disorder. Lethal catatonia and malign hyperthermia included in hy-

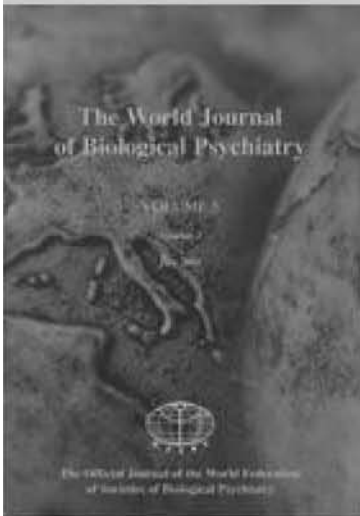
perthermic syndromes related to medication were excluded because of diaphoresis, muscle rigidity, elevated CK, leukocytosis and history of antipsychotic use (Kaplan and Sadocks 2003). Although both lethal catatonia and neuroleptic malignant syndrome (NMS) have similar signs or symptoms, discontinuation of the antipsychotic drug usually results in resolution of NMS. The important clue for settling on a diagnosis was that the patient had never been administered an antipsychotic medication until the application of ziprasidone. The use of diazepam and biperiden was the simplest and most effective way of administration in an emergency situation, so that no time was lost in beginning the treatment. There are several publications which show the use of biperidene in NMS treatment (Unal et al. 1996; Hasan et al. 1999; Yumru et al. 2006). We began treatment with daily administration of intravenous diazepam (15 mg/day) and biperiden (15 mg/day) after the diagnosis was made. Doses were the same until the day of discharge. Gradual decrements, 5 mg/day decreased for a week, were planned. Diazepam and biperiden were given orally from discharge onwards, and by the third week, 14 days later, the administration of these agents was stopped. The gradual resolution of NMS symptoms was well documented, ending on the 10th day. The ESRS Parkinsonism subscale score was 28 on the first day of admission. By the 11th day after admission, the ESRS parkinsonism subscale score decreased to 0, and the patient was discharged.

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