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# The World Journal of Biological Psychiatry

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### Instructions to Authors

## Editorial

### A Psychopathological Marker or Biological Psychiatry

It is always a goal to any clinical investigator to identify a symptom or a cluster of symptoms for the definition of a disease. The 'target symptom', the 'essential symptom', the 'primary symptom', the 'nuclear symptom', etc., have been some of the expressions given to the phenomenon that would produce the clue for the correct diagnosis. Sometimes this task can be carried out properly, for example, the sign of jaundice for hepatitis, a Blumberg signal for peritonitis, or even a Veraguth signal for endogenous depression.

Many have tried to identify a clear sign or symptom for schizophrenia. Modern classifications base the diagnosis of schizophrenia on Schneider's first rank symptoms. But even considering the whole clinical picture, a first rank symptom is not a safe indication for the diagnosis of schizophrenia. On the other hand, until now, no somatic marker has been identified to definitely support the diagnosis of schizophrenia. As is well known, in terms of this enigmatic disease we continue in a confusional state, like walking in a fog, changing direction according to the most strong immediate propagated data, very often coming back to the same point. Of course, we are also touching important elements, which will one day complete the final picture. However, it requires hard work to proceed having just a more or less strong impression.

Genetic or other biological methods are expected to help make more reliable diagnoses or subclassifications in the near future. However, until this time arrives, we should try to resolve the issues with the current tools. It is always necessary to repeat that, also in biological psychiatry, psychopathology is the first and essential tool.

Ninety years ago Karl Jaspers coined a simple expression to represent the change in personality occurring in the schizophrenic patient: 'something new'. Jaspers called this phenomenon the result of a 'psychic process'. 'Psychic process' is a concept based only on psychological elements and presenting some similarity with the organic process (cerebral process). Jaspers' definition for 'psychic process' is: changes in the psychic life, the personality becoming diverse from the anterior one and in an irreversible mode. The great psychopathologist used to say that a major problem is the recognition of the relation between the 'psychic process' and the subjacent 'cerebral process', which he called 'direct parallel process'. Nowadays, research is very much focussed on the 'cerebral process' (from molecular biology to genetics, neurophysiology, neuropathology, etc.), completely ignoring the 'direct parallel process', or in another language, what makes (and how) the 'disable' brain promoting the 'psychic symptoms'. Under that perspective, schizophrenia (the psychopathological features) would be nothing more than the consequence of the 'direct parallel process'.

I would like to draw your attention to part of that intricate problem. I would like to highlight the 'something new'. Many times it is relatively comfortable for the psychiatrist to recognise a personality changed by schizophrenia, however, we are rarely able to identify the moment of that change. As an example, we could say that the so-called late-onset schizophrenia means only that we were not able to identify the correct moment of the transformation in the personality, possibly happening at a younger age. It is reasonable to assume that the recognition of this moment will give an indication for more precise research in terms of which stage of brain development is implicated in the disease, as well as the genetic process involved in that phase of life (the 'genetic clock').

'Something new' represents the result of a crucial transformation in the personality at a certain point in life, and according to its characteristics and sequence as a 'psychic process', it can be recognised as happening at the 'point of no return'. Therefore, evolving from Jaspers, we should try to establish this 'point of no return' and then investigate the 'cerebral process' at that stage.

How can we reach the 'point of no return'? When a person comes to a psychiatrist, the schizophrenic process has already started sometime previously. It has also been recognised that the family or other persons close to the patient are only able to identify the process after a period of time. The most favourable situation for the psychiatrist would be the observation of the sequence of the initial phase (so diverse in its presentation). One way to reach the 'point of no return' is through the patient's consciousness. How is the consciousness of a schizophrenic? At that point, the focus is not the disease itself, but the way the patient presents himself or herself in terms of consciousness, the way the patient perceives him or herself, the others and the world. Stimulating self-descriptions promote a critical self-consciousness that becomes broader and deeper as the time goes.

The studies of 'Comprehension' by Wilhelm Dilthey give a theoretical reference to analysing the schizophrenic consciousness. 'Comprehension' means an intuitive (immediate) knowledge, a natural disposition of human being. 'Comprehension' is a psychological apprehension considering the connections of life events. 'Comprehension' means knowledge with a meaning referred specifically to a person in a situation, including a teleological sense. How is the capability of comprehension in the schizophrenic? It is definitely changed. The psychological apprehension is almost completely replaced by causal relationships; the teleological sense is replaced by an analysis of the concrete appearance. Consequently, the patient lacks empathy and the acts lack intentionality. The patient conducts himself moved by causal laws.

In making the patient look at his consciousness, this will give him a chance to realise that he is someone that has structurally changed in his personality; then, he is able to detect the 'point of no return' to the previous way of being; he is able to perceive himself as a person who is no longer capable to spontaneously practice the transposition mechanism, it means, to be in the other's place and feel and think like the other, and to participate. The schizophrenic is able to realise that life is now moving according to the immediacy of sensations, without taking into consideration the continuous spiralled movement of life and the intentionality of the events. He becomes reduced to the concrete appearance of life.

The 'something new' is the manifestation of the disturbance of comprehension we find in the schizophrenic. The 'something new' refers to the irreversible change in the personality that occurs in the 'point of no return' and can be self-identified.

The longitudinal (biographic) perspective brings opportunity to research the patient's consciousness. The phenomenological psychopathological study of the schizophrenic's consciousness appears to give opportunity to reach what can be a nuclear phenomenon in schizophrenia: the peculiar disturbance in the capability of comprehension.

If we are dedicated to exploring the schizophrenic consciousness through the consciousness of the patient, we are able to identify the 'point of rupture' in the vital curve and explore the changes in the capability of comprehension. In this sense, the irreversible change in the capability of comprehension could be understood as a psychopathological marker for schizophrenia, and a significant indicator of the crucial moment of the beginning of the schizophrenic process.

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## The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders, Part II: Treatment of Mania

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### Summary

Identical to the preceding guidelines of this series, these practice guidelines for the biological, mainly pharmacological treatment of acute bipolar mania were developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). Their purpose is to supply a systematic overview of all scientific evidence pertaining to the treatment of acute mania. The data used for these guidelines have been extracted from a MEDLINE and EMBASE search, from recent proceedings of key conferences, and from various national and international treatment guidelines. Their scientific rigor was categorised into four levels of evidence (A-D). As these guidelines are intended for clinical use, the scientific evidence was finally not only graded, but has also been commented by the experts of the task force to ensure practicability.

**Key words:** bipolar disorder, mania, acute treatment, evidence-based guidelines, pharmacotherapy, antipsychotics, mood stabiliser, electroconvulsive therapy.

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### Introduction and Methods

This part of the WFSBP guidelines for the pharmacological treatment of bipolar disorder is dedicated to mania. The background and reasons for establishing these treatment recommendations were explained in the first part, dedicated to the treatment of bipolar depression (Grunze et al. 2002). In brief, the following grading of

evidence based on the Schizophrenia Patient Outcome Research Team (PORT) treatment recommendations (Lehman and Steinwachs 1998) was established, combining evidence-based elements and clinical experience, and used in both the WFSBP guidelines on bipolar (Grunze et al. 2002) and those on unipolar (Bauer et al. 2002) affective illness:

**Level A:** Good research-based evidence. This means that evidence for efficacy has been proven by at least three methodologically good trials, including at least one placebo-controlled trial and at least two comparison trials with another standard treatment. In these trials, criteria such as sufficient sample size, duration of trial, randomised distribution to either treatment and double-blind conditions should have been obeyed.

**Level B:** Fair research-based evidence. On the basis of trials, this includes evidence from at least two randomised, DB-controlled trials which, however, fail one criterion to fulfil the criteria above (e.g., small sample size or no placebo control) or from 1 RDB study and at least 1 prospective, large scale naturalistic study.

**Level C:** 1 RDB study with comparator, 1 prospective open label (POL) study, or 2 POLs with >10 participants.

**Level D:** Recommendation based on prospective case studies with a minimum of ten patients or large scale retrospective chart analyses and support by expert opinion.

According to clinical opinion, acute mania can be differentiated into euphoric (classical) mania, dysphoric mania, mixed states, mania with psychotic or catatonic features, and mania within a rapid cycling course of the disease. If these subtypes can be shown reliably to exist (Dilsaver et al. 1999), they may influence not only classification but also the choice of treatment.

Clinical experience with the various tentative mood stabilisers over recent years has suggested that a drug that is efficacious in one manifestation of mania is not necessarily the treatment of choice for the overall spectrum of mania. In recognition of this sentiment, these treatment algorithms will also distinguish between euphoric (classical) mania, dysphoric mania and mixed states, psychotic mania, mania within a rapid cycling course of bipolar disorder and, finally, hypomania. However, words of caution are necessary. Manic states are certainly not monolithic, but neither are they likely to reflect neat clinical distinctions. Recent factor analysis of symptoms in mania suggested that there are perhaps five factors that contribute to the syndrome (Cassidy et al. 1998). The first and strongest factor represented dysphoria in mania, with strong positive loadings for depressed mood, lability, guilt, anxiety and suicidal thoughts and behaviours, and a strong negative loading for euphoric mood. Factors 2 through 5 represented

psychomotor acceleration, psychosis, increased hedonic function and irritable aggression, respectively. The distribution of weighted scores on factor 1 was bimodal, whereas the corresponding distributions of factors 2 through 5 were unimodal. No general factor denoting overall severity of mania was found. These results were from a modest sized sample. Subsequently the same authors have claimed that Grade of Membership (GOM) analysis revealed five 'pure types' with good face validity. The major new finding was of two mixed mania presentations. The first of these displayed a dominant mood of severe depression with labile periods of pressured, irritable hostility and paranoia, and the complete absence of euphoria or humour. The second mixed mania displayed a true, incongruous mixture of affects: periods of classical manic symptoms with euphoria, elation, humour, grandiosity, psychosis, and psychomotor activation, switching frequently to moderately depressed mood with pressured anxiety and irritability. DSM-III-R criteria (used to classify the patients originally) did not reliably identify either of these two natural groups of mixed bipolar patients (Cassidy et al. 2001). While different sub-classes of mania may exist, all the extant data on differential treatment response represent potentially unreliable secondary analysis of data sets lacking power to prove that different responses to different treatments are real, not imaginary.

#### Treatment of acute mania

##### • Euphoric (classical) mania

Traditionally, bipolar I disorder with euphoric mania was considered as the classical and, for a long time, only type of mania that justifies the diagnosis of bipolar disorder. Other manifestations within the bipolar spectrum, e.g. bipolar II disorder or bipolar disorder with psychotic mania, were often classified either as recurrent depression or schizophrenia. Until recently, most studies on antimanic agents were exclusively conducted in patients with bipolar I disorder and euphoric mania, resulting in firm evidence that especially lithium is effective in this type of mania. Our literature search found 26 studies, of which at least 13 are controlled trials in which lithium showed superior or equal efficacy compared to placebo (five trials), antipsychotics, carbamazepine or valproate in the treatment of acute euphoric mania (for a review, see Bowden 1998; Poolsup et al. 2000; McElroy et al. 1996b). The only methodological pitfall is that, so far, only one three-arm study with placebo control and active comparator has been published for lithium (Bowden et al. 1994). Nevertheless, with evidence considered, lithium can be seen as a first line treatment in euphoric mania within classical bipolar I disorder (level A). Other level A qualifying treatments include in particular valproate (Emrich et al. 1980; Freeman et al. 1992; Pope et al. 1991; Bowden et al. 1994) and some atypical antipsychotics,

especially olanzapine (Tohen et al. 1999; Tohen et al. 2000). Compared to lithium, valproate has a more rapid onset of action as valproate's wide therapeutic window allows loading treatment strategies (Keck et al. 1993). When compared directly to lithium, valproate showed approximately equal efficacy (Bowden et al. 1994; Emilien et al. 1996). Especially in patients with numerous (>8) episodes in history (Swann et al. 2000a), or >4 depressive episodes (Swann et al. 2000b) and who have failed on lithium prophylaxis, valproate may be the preferred choice in the treatment of acute euphoric mania.

Recently, the atypical antipsychotics olanzapine (Tohen et al. 1999; Berk et al. 1999; Tohen et al. 2000) and risperidone (Sachs et al. 2002; Yatham 2000; Segal et al. 1998) supplied Level A evidence for antimanic efficacy. Also ziprasidone has shown antimanic properties in an unpublished controlled trial in bipolar patients (Keck and Ice 2000, Level C). Olanzapine has already been approved by the FDA for the treatment of mania.

There are doubts about the clinical relevance of all recent placebo-controlled trials in mania. They are dominated by excessively high drop-out rates (about 50% in three weeks) and the reliance on rating scales with "last observation carried forward." Additionally, there is as yet very little experience of how the newer atypical antipsychotics compare directly to other treatment standards. Thus, for olanzapine there is a small, but not placebo-controlled study against lithium (Berk et al. 1999) and two inconclusive – due to insufficient dosages – studies against valproate. The arguments for the use of atypical antipsychotics in general are their good tolerability when used at doses recommended for schizophrenia (which may be too low for severe mania) and relatively rapid onset of action. However, their potency in treating acute mania has still to be established, especially in comparison with typical antipsychotics.

Our own literature quest found at least 17 double-blind controlled studies examining the efficacy of either carbamazepine or oxcarbazepine in acute mania, however, carbamazepine has never been tested against placebo in a parallel group design (Licht 1998). Carbamazepine may be useful in selected patients in treating euphoric mania (Level B, for a review Keck and McElroy 1996; Post et al. 1996; Emilien et al. 1996), and should be continued especially in those who have previously been on prophylactic treatment with carbamazepine. Otherwise, it does not seem to have any special advantage over the other treatment alternatives. In fact, a recent small controlled study demonstrated a better efficacy for valproate than carbamazepine in acute mania (Vasudev et al. 2000). The use of carbamazepine is also complicated by its interaction with other co-

medication, e.g. antipsychotics, through effects on the cytochrome P450 system (Hesslinger et al. 1999), leading to a marked decrease of antipsychotic plasma levels and probable loss of efficacy.

Taken together, the evidence for efficacy in euphoric mania is very good (Level A) for lithium, valproate, olanzapine, risperidone, reasonable for carbamazepine (Level B) and supposedly for ziprasidone (Level C). Classical, highly potent antipsychotics are almost universally used and evidence exists that they are efficacious (Level A, for a review see Tohen and Zarate 1998; Dubovsky and Buzan 1997). This has recently been backed up by a double-blind randomised study of risperidone as add-on to mood stabilisers where haloperidol was an internal comparator (Sachs et al. In Press). In this study, haloperidol was significantly better than placebo. The position of the older antipsychotics remains anomalous because the quality of the research evidence for any given drug is individually surprisingly weak: haloperidol, for example has never been formally shown to be superior to placebo in a parallel-group monotherapy trial in mania, yet it is 'gold standard' treatment besides lithium.

However, the use of classical neuroleptics *in high dosages* should be restricted to very severe or violent cases of mania where parenteral administration is the only choice, and should be limited to a maximum of a few weeks, to avoid the risk of tardive dyskinesia (TD). TD may have an increased incidence in bipolar patients (Mukherjee et al. 1986). The aetiology of TD remains uncertain but is believed to result from long-term blockade of dopamine receptors. The true risks for atypical antipsychotics with a high degree of D2 receptor occupancy are not yet established. The key message from the introduction of the atypical drugs is that it is possible to achieve antipsychotic and anti-manic action without inducing severe extra-pyramidal side effects. This may imply that low-dose classical antipsychotics are a sensible alternative to atypical antipsychotics (Geddes et al. 2000). This may apply as much to mania as to schizophrenia.

##### • Dysphoric mania and mixed states

These two manifestations of mania are summarised under one heading. According to DSM-IV, mixed states imply that diagnostic criteria for a manic episode and a depressive episode (except for the duration criterion) are fulfilled simultaneously. Dysphoric mania describes mania with some depressed and dysphoric features that are either not pronounced enough or insufficiently lasting enough to fulfil the criteria for a major depressive episode. Women appear more often affected than men (Arnold et al. 2000).

As dysphoric mania and mixed states have not been the subject of intensive studies and

controlled trials so far, we have only a limited amount of evidence for the superiority of one drug over another. Thus secondary analysis of the influential valproate efficacy study (Swann et al. 1997a) as well as some older studies (Secunda et al. 1987; Himmelhoch and Garfinkel 1986) indicated that lithium may not be very effective, and that valproate, carbamazepine, olanzapine and risperidone may be more efficacious than lithium in these patients (Freeman et al. 1992; Swann et al. 1997b; Goldberg et al. 1998; Tohen et al. 2000; Benabarre et al. 2001, Level C). The use of classical antipsychotics especially in higher dose may exacerbate dysphoric or depressive experience and should probably be avoided (Whitlock and Evans 1978).

#### • Psychotic mania

Psychotic mania has only recently been arbitrarily designated as a subtype of bipolar mania. It is unclear whether secondary grandiose delusions – the commonest clinical manifestation of ‘psychosis’ merits qualitative distinction since it looks much more like an expression of severity. On the other hand, first rank symptoms also occur in mania and confuse the distinction from schizophrenia. ‘Psychotic mania’ is a diagnosis that conflates these perhaps different clinical conditions.

As for mixed states, so for psychotic mania evidence for superiority of one treatment over another is limited. Classical antipsychotics, in this case pimozide, may be superior to lithium as shown by the Northwick Park functional psychosis study (Johnstone et al. 1988). Some guidelines favour anticonvulsants over lithium when psychotic symptoms are present (e.g. Kusumakar et al. 1997), others recommend the combination of either valproate or lithium with an antipsychotic right from the start (Keck and McElroy 1996). As far as monotherapy studies are concerned, valproate showed equal efficacy to haloperidol in one randomised but not blinded trial in psychotic mania (McElroy et al. 1996a, Level C). Although it is tempting to assume that all atypical antipsychotics are efficacious in psychotic mania, unambiguous controlled trials are still missing. However, retrospective analysis of the two placebo-controlled trials of olanzapine and of the controlled studies involving risperidone showed similar response rates in psychotic versus non-psychotic mania (Level C).

#### • Severity of mania

Recent treatment recommendations from North America have almost uniformly advocated the preferential use of lithium or valproate (‘mood stabilisers’) for the first-line treatment of mania. Despite this, classical antipsychotics are still very widely used in manic patients. For example, more than 60 % of manic patients received classical antipsychotics at the Psychiatric University Hospital of Vienna between 1997 and

1999 (Letmaier, personal communication). In other settings, the figures may be even much higher (for example, 89 % in a Scandinavian routine setting, Licht et al. 1994).

Obviously, besides symptomatology, the severity of behavioural disturbance determines the first-line treatment in acute mania. Most treatment algorithms are based on controlled trials in mild to moderately manic patients who are still able to sign informed consent. In clinical practice, severity is more likely the primary argument in favour of a special drug. For the ultra-short treatment of acutely manic and highly excited or violent patients, classical antipsychotics still have their place (Licht 1998) and are superior to lithium (Prien et al. 1972; Garfinkel et al. 1980). In patients who are severely manic but still willing to take medication, loading with lithium (Keck et al. 2001), valproate (Keck et al. 1993; Grunze et al. 1999) or carbamazepine may be an alternative (Dose and Emrich 1995).

Although atypical antipsychotics showed efficacy in controlled trials, these trials included mild to moderate manic patients and generalisability to severe mania is difficult (Licht et al. 1997). Clinical experience with dose-loading is still missing and may be complicated by potential QT prolongation. Currently, the domain of atypical antipsychotics appears to be milder forms of mania and hypomania. An exception may be clozapine which has shown efficacy in refractory mania, both euphoric and dysphoric, in open prospective trials (Level C, Calabrese et al. 1996; Green et al. 2000; Müller and Heipertz 1977; Suppes et al. 1992; Antonacci and Swartz 1995).

#### • Hypomania

Hypomania usually does not need immediate intervention with a maximised treatment. The best recommendation is to check the plasma level of the mood stabiliser the patient has been taking previously and, depending on the result, increase the dosage. If the patient has not previously received a mood stabiliser, an appropriate drug should be introduced that will also be the drug of choice for prophylaxis. As many patients with hypomania may have an underlying cyclothymic disorder, drugs showing efficacy in cyclothymia should also be considered and continued for long-term treatment. Open studies suggest efficacy of low doses of lithium or valproate (Deltito 1993; Jacobsen 1993; Akiskal 2001). There is also evidence for the usefulness of risperidone in hypomania (Vieta et al. 2001). If no further prophylaxis is planned, short-term treatment with either valproate or an atypical antipsychotic may be the best choice (Level D), as both are well tolerated, have a good safety profile and a relatively rapid onset of action, minimising the danger that hypomania develops into mania within the next days.

#### • Mania within a rapid cycling course of bipolar disorder

The treatment of rapid cycling patients is a special challenge (Knoll et al. 1998). There is increasing awareness of the switch risk associated with the use of classical antidepressants and the risk of kindling the rapid cycling course (Wehr and Goodwin 1979; Altshuler et al. 1995). The failure of lithium treatment appears high in rapid cycling patients (Calabrese and Woysville 1995). Unfortunately, there have been no double-blind controlled studies specifically dedicated to the acute treatment of mania within a rapid cycling course. However, there is a large bulk of open data which favour valproate for the treatment of mania within rapid cycling, with the largest naturalistic follow-up being reported by Calabrese (Calabrese et al. 1993) (Level C). Carbamazepine also has been reported to be effective in rapid cycling (Joyce 1988) (Level D). In refractory patients, clozapine (Suppes et al. 1994; Calabrese et al. 1991; Frye et al. 1996; Lancon and Llorca 1996) or a combination therapy with valproate and lithium may also be useful (Sharma et al. 1993) (Level D). If not only the acute treatment of break-through mania is an issue, but also maintenance treatment, initiation of lamotrigine with subsiding (hypo)mania can be recommended, especially in bipolar II patients (Calabrese et al. 2000).

Finally, rapid cycling appears more common in patients with hypothyroidism, and high-dose thyroid hormone augmentation may be considered already at an early stage of treatment (Bauer and Whybrow 1990; Bauer et al. 1990)

#### Tolerability and safety

The treatment experience is a key issue for patients and their families. It also has inevitable consequences for trust in the therapeutic relationship and compliance. Extra-pyramidal side effects (EPS) and long-term TD are the major risks of using dopamine blocking drugs. In the case of mania, high doses of classical antipsychotics, a traditional approach in many countries over many years, should not be the treatment of choice in the great majority of patients who accept medication and should only ever be used when the potential benefits definitely outweigh the known risks. Low doses up to the threshold for EPS may be acceptable, if sufficiently monitored, but increasingly we expect atypical drugs to prove preferable where they can be afforded.

Patients who take drugs irregularly, and who are at a risk of overdosing, should not be considered as candidates for lithium treatment owing to its narrow therapeutic ratio.

There is a growing awareness of the secondary impact of many long-term treatments on general physical health. Apart from being a cosmetic

issue, obesity is increasingly seen as a major health issue for patients treated with drugs that promote weight gain, of which there are many examples in any bipolar guideline. While this is a concern that is most pressing in the nations of the world where obesity is already prevalent, it is a potential problem for all individuals who gain weight excessively after drug treatment. Valproate, lithium and several antipsychotics all cause significant weight gain in long-term treatment. With weight gain go other adverse metabolic effects (e.g. carbohydrate intolerance/type II diabetes and hyperlipidaemia) and hypertension. When combined with heavy smoking, an additional hazard for many patients with mood disorder, cardiovascular disease is a major long-term risk. Not only for tricyclic antidepressants, but also for a variety of antipsychotics prolongation of the QT interval may constitute a minor additional problem. Appropriate medical screening and advice should constitute part of good psychiatric care. Thus, not only efficacy is an issue when selecting the first-line treatment, but also the patient's special needs and vulnerability to side effects.

Adverse effects are otherwise specific to individual drugs and usually require drug withdrawal. Readers are referred to relevant data sheets.

When considering special populations, all classical mood stabilisers (lithium, valproate, carbamazepine) appear teratogenic in pregnancy, especially in the first trimester, and if possible use should be interrupted. On balance lithium is now believed to be safer than the anticonvulsants (Cohen et al. 1994). Benzodiazepines and typical antipsychotics have a reasonable safety profile and can be used as a rescue medication in break-through mania. There is increasing awareness of the early onset of bipolar disorder (Kessler et al. 2001). In adolescence, some experience exists with lithium, valproate, carbamazepine and atypical antipsychotics (James and Javaloyes 2001; Kowatch et al. 2000; Chang and Ketter 2000). In geriatric patients, the use of lithium should be considered very carefully due to decreased kidney function, diminished fluid intake and probably more pronounced cognitive side effects. Valproate or low dose atypical antipsychotics may be more favourable (Amann et al. 2000).

#### Other treatment options

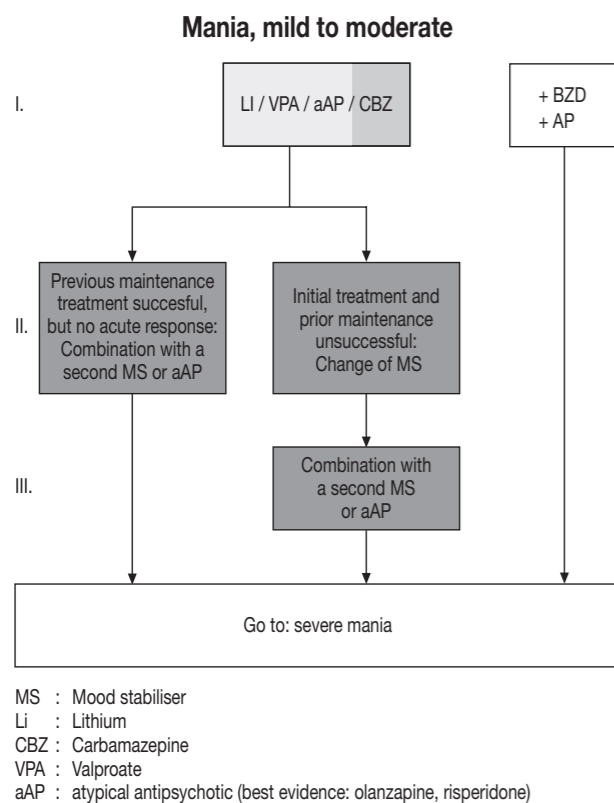
Small open studies and case reports exist on numerous alternate pharmacological approaches (for example, anticonvulsants such as phenytoin, oxcarbazepine, gabapentin, clonazepam, zonisamide, topiramate; carbonic anhydrase inhibitors, PK-inhibitors (e.g. tamoxifen), omega-3 fatty acids, calcium antagonists, clonidine, methysergide, etc.), but the evidence is still very limited.

Electroconvulsive therapy (ECT) is regarded as the most efficacious treatment modality for mania, frequently chosen (and anecdotally found effective) when other approaches have failed (Small et al. 1988; Black et al. 1987; Mukherjee et al. 1994, Level C). Accordingly it should be considered in patients accepting this treatment and who have not responded to previous drug treatments. Case reports on the efficacy of transcranial magnetic stimulation in mania exist (Yaroslavsky et al. 1999; Pridmore and Belmaker 1999), but this may be difficult to conduct, at least in severely manic patients. The same may be true for more sophisticated psychotherapeutic interventions besides very basic behavioural standards (correcting sleep-wake cycle, avoid hyperstimulation, etc.).

**Conclusion**

The most important steps in the state-of-the-art treatment of mania include

- clarification of the subtype of mania,
- considering the longitudinal course of illness,
- although treatment is often initiated against the patient's will, at a later stage the patient's compliance should be optimised by using a



MS : Mood stabiliser  
 Li : Lithium  
 CBZ : Carbamazepine  
 VPA : Valproate  
 aAP : atypical antipsychotic (best evidence: olanzapine, risperidone)

Additionally, when needed:  
 BZD : Benzodiazepines  
 AP : Antipsychotics (preferably low potent or atypical AP)

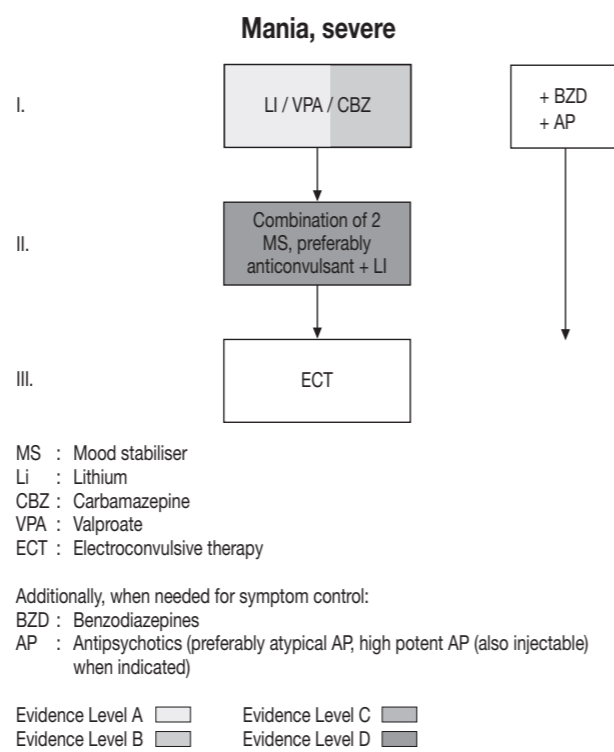
Evidence Level A  Evidence Level C   
 Evidence Level B  Evidence Level D

**Figure 1**

drug with a favourable tolerability profile for the individual patient.

If the patient has been on prophylactic treatment, with reasonable success and good tolerability so far, an increase of the dosage of this previous mood stabiliser should be considered first. Otherwise, if the patient has had no previous prophylactic treatment and prophylaxis may become an issue, the overall course of the disease should also be taken into consideration. Clearly, prophylactic treatment of a patient with classical bipolar I disorder with only rare episodes differs from prophylactic treatment in a rapid cycling patient showing additional atypical features like psychotic mania. Whereas in the first case, lithium may be the treatment of choice already for acute mania, non-classical manifestations seem to respond better to anti-convulsants and perhaps atypical antipsychotics.

Suggestions for step-wise pharmacological treatment algorithms are summarised in the Figures 1 and 2 below.



**Figure 2**

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## Testosterone Deficiency and Mood in Aging Men: Pathogenic and Therapeutic Interactions

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### Summary

In contrast to women, men do not experience a sudden cessation of gonadal function comparable to menopause. However, there is a progressive reduction in hypothalamic-pituitary-gonadal (HPG) function in aging men: testosterone (T) levels decline through both central (pituitary) and peripheral (testicular) mechanisms and there is a loss of the circadian rhythm of T secretion. In cohorts of men 75 years of age, mean plasma T levels are 35% lower than comparable young men, and more than 25% of men over 75 appear to be T-deficient. Such age-associated T deficiency, which has been termed 'andropause', is thought to be responsible for a variety of symptoms experienced by elderly men, such as weakness, fatigue, reduced muscle and bone mass, impaired haematopoiesis, oligospermia, sexual dysfunction, depression, anxiety, irritability, insomnia and memory impairment. However, it has been difficult to establish correlations between these symptoms and plasma T levels. Nevertheless, there is some evidence that T replacement leads to symptom relief, particularly with respect to muscle strength, bone mineral density and haematopoiesis. Studies to date on the specific association between psychiatric symptoms, such as depressed mood, and T levels have been methodologically flawed. Overall, data suggest that although hypogonadism is not central to major depressive disorder (MDD), HPG hypofunction may have aetiological importance in mild depressive conditions, such as dysthymia.

**Key words:** andropause, testosterone deficiency, depression, male, geriatric.

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### Introduction

Male HPG function declines progressively with age, and a substantial proportion of men older than age 50 have testosterone (T) levels below the normal range (Vermeulen et al. 1995). Mild T deficiency in elderly men can, therefore, be considered physiological (i.e. a para-aging phenomenon) or pathological (i.e. a deficit state). Currently, since age-adjusted norms are not used, it is treated as pathological. Yet, even if physiological, such a decline may be clinically significant, as with the age-associated decline in female gonadal hormones, or menopause.

The effects of T deficiency are similar to those of the aging process itself: decreased musculo-skeletal mass, increased adipose deposition, decreased haematopoiesis, decreased facial hair growth, as well as decreased libido, energy, mood and memory (Villareal and Morley 1994; Vermeulen et al. 1996). Testosterone replacement consistently reverses these sequelae in younger hypogonadal men (i.e. ages 20-60): body weight, fat-free muscle mass, muscle size and strength increase; continued bone loss is prevented; sexual function and secondary sex characteristics (e.g. facial hair) are restored and maintained; and haematocrit increases (Burriss et al. 1992; Snyder et al. 2000). The application of a T replacement strategy for older men with low or low-normal T levels is thought by some investigators to be especially promising for reversing the aging effects on bones and muscle mass, as well as for enhancing mood, energy, cognition and libido (Morley 2000). Yet, it has been difficult to correlate hormone levels with such age-related phenomena (Morales et al. 2000; McKinlay et al. 1989). Moreover, there are only limited controlled data on the effects of T replacement in elderly men (Snyder et al. 1999a, 1999b), and none that address psychiatric symptoms in this age group. Specific studies in aging men are particularly important, since age-related T deficiency is generally more modest than the profound hypogonadism seen in T replacement trials with younger men. In this article, we review male HPG psychophysiology and then focus on the relationship between HPG axis functioning and depression in elderly men.

### Male HPG physiology

The testes and adrenals secrete several male sex hormones, called androgens. All are steroid hormones – i.e. derived from cholesterol and

containing a basic skeleton of four fused carbon rings. Testosterone is the most potent and abundant androgen. Secretion occurs in pulsatile bursts, and is regulated through a negative feedback on the hypothalamus and pituitary (Figure 1). In the circulation, approximately 98% of T molecules are protein bound: just over half are weakly bound to albumin, and the remainder are tightly bound to sex hormone-binding globulin (SHBG). Free T diffuses into target cells, where it is converted to two active metabolites: dihydrotestosterone (DHT) and estradiol (E<sub>2</sub>). There is tissue variability in the concentration of the cytoplasmic enzymes required for this conversion, 5 $\alpha$ -reductase and aromatase, respectively, and differential tissue sensitivity to each of these metabolites. Both T and DHT bind to the androgen receptor. The steroid-receptor complex binds to specific sequences of genomic DNA, which thereby influences messenger RNA production and modulates synthesis of a wide array of enzymatic, structural, and receptor proteins. In addition, T influences cellular activity in a nongenomic manner through activation of the membrane and membrane receptors, and second messengers (Bagatell and Bremner 1996; Guo et al. 2002).

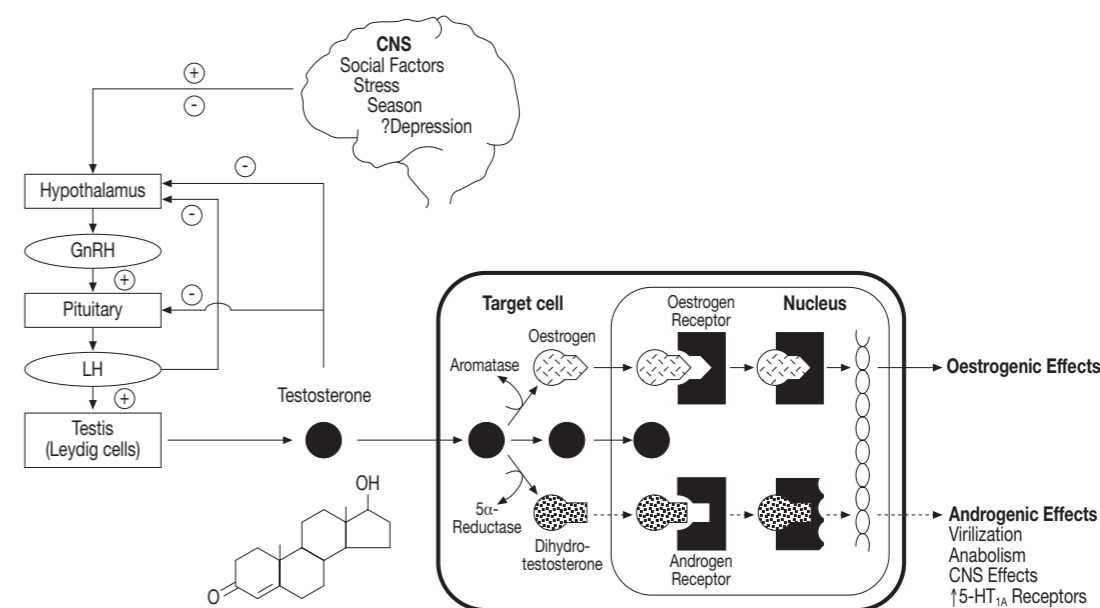
In a comprehensive meta-analysis, Gray and colleagues (1991) used 44 studies that met stringent criteria for reporting the relationship between mean T level and age. They confirmed a progressive decline in T level with age. In a multiple regression model, the best predictors of both T level and the slope of the age-related decline were good general health status and morning serum sampling (both of which predicted higher levels and steeper slopes). This was probably due largely to the blunting of the

circadian early morning peak that occurs with age and illness. Overall, the decline in free T, about 1% per year after age 40, was about twice that of total T.

### Male HPG axis, mood, cognition, and age

**• Neuropsychiatric effects of testosterone**  
Testosterone's influence occurs at multiple levels: metabolic processes, peripheral (particularly genital) tissues, the spinal cord and the brain (Schmidt and Rubinow 1997). Non-specific metabolic effects (e.g. increased hematocrit, anabolism) and/or stimulatory effects on genital tissue could indirectly influence neuropsychiatric functioning (e.g. via increased general arousal). Specific CNS activation occurs via binding of androgen receptors by testosterone or DHT, oestrogen receptors by estradiol, and through membrane-associated actions (Guo et al. 2002). Various androgen-related topics that have been well-reviewed elsewhere include the psychiatric effects of high-dose anabolic steroid abuse (Pope et al. 2000); the use of DHEA as a marker of psychiatric health and as a treatment for mood and/or sexual problems (Wolkowitz et al. 2000); the use of testosterone for sexual problems in men and women (Seidman 2000); and the neurocognitive effects of androgens in women (Sherwin and Gelfand 1987).

Experimental evidence has demonstrated that androgens directly influence sexual behaviour, aggression and dominance in mammals, including non-human primates. These direct effects appear to be more influenced by social factors in primates. For example, in a multi-male group of rhesus macaques (*Macaca mulatta*), castration leads to an immediate reduction in



**Figure 1**  
The male hypothalamic-pituitary-gonadal axis

sexual behaviour; in a single-male-multiple-female group, post-castration sexual behaviour declines after one month; and in a male-female pair, reduced sexual activity does not occur until two months after T suppression (Wallen et al. 1991). In human males, direct behavioural effects of androgens are less apparent, and likely to be even more influenced by social factors. Nonetheless, consistent evidence supports an androgenic influence on human sexual behaviour, aggression, and cognition.

#### Sexual behaviour

The best established testosterone-behaviour relationship in human males is with sexual function: increasing plasma androgens at puberty is correlated with the onset of nocturnal emission, masturbation, dating and infatuation. Males with an early onset of androgen secretion, i.e. precocious puberty, often develop in parallel an early interest in sexuality and erotic fantasies (Feder 1984). Most striking, T replacement of hypogonadal men leads to a dramatic increase in sexual desire, sexual activity and frequency of erections (Anderson et al. 1992). Suppression of T secretion in eugonadal men leads to reduced sexual desire and activity, and a decrease in spontaneous erections (Bagatell et al. 1994). There appears to be a threshold (which varies from person to person) below which sexual function is impaired.

#### Aggression

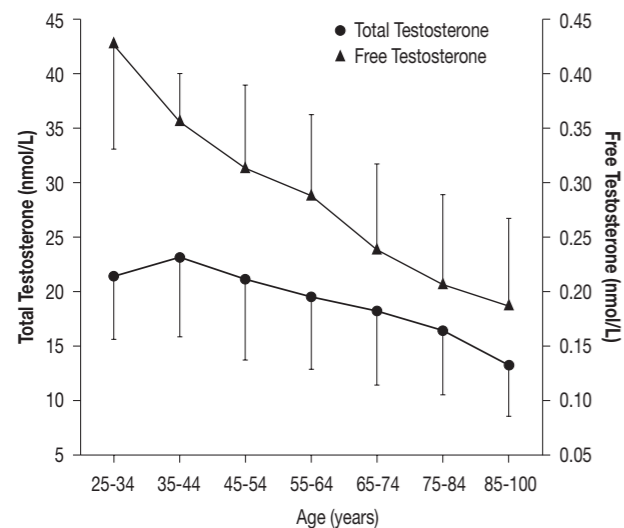
Testosterone appears to play some role in aggression, though social factors have a strong influence. Anti-androgens have been used to reduce aggressiveness in male sex offenders, though data supporting its success (i.e. reduced recidivism) are inconsistent (Cooper 1995; Grossman et al. 1999). Numerous correlational studies have examined the relation between

plasma T level and measures of aggression in human males (Archer 1991; Olweus et al. 1988). Interpretation of these studies is limited by the variability in social context, and moreover, by the known increase in T that occurs as a result of aggressive encounters (Archer 1991). Furthermore, studies have differed in measures of aggression used – i.e. actual behaviour versus aggressive traits – and subject characteristics, and cannot be easily summarized. Some investigators have reported positive correlations between T level and some aspects of aggression, especially among subjects selected on the basis of violent behaviour (i.e. male prisoners) (Archer 1991; Olweus et al. 1988; Dabbs et al. 1996). Others have not found any correlation between T level and multiple aspects of aggression (Olweus et al. 1988). In a comprehensive review of the topic, Archer (1991) concluded that: 1) consistent evidence suggests that violent male offenders have significantly higher T levels than less violent individuals; and 2) there is a small but statistically significant correlation between T level and hostility in a variety of male populations, which is stronger when aggressiveness is rated by others in the person's social environment compared to self-assessment.

#### Cognitive functioning

Spatial cognition – i.e. those tasks that include visual perception, spatial attention, object identification or visual memory processes – is a sexually dimorphic cognitive function (Collins and Kimura 1997). Women excel at tasks requiring fine motor dexterity or verbal fluency, and men excel on block rotation tasks and on embedded figures tests. In studies assessing the relationship between T level and cognitive performance among young adult men with normal T levels, four well designed studies have demonstrated a positive correlation between spatial ability and T level (Gordon and Lee 1986; Gouchie and Kimura 1991; Hannan et al. 1991; Christiansen Knussmann 1987), and in one of these (Christiansen and Knussmann 1987) a negative correlation between T level and verbal ability.

Three well-designed correlational studies have been performed in elderly men. In a small study, 30 healthy men (mean age 69 years) completed five cognitive tests measuring verbal memory, spatial memory, verbal fluency, mental rotation and susceptibility to interference. The only significant association demonstrated was a negative correlation between total T and verbal fluency ( $r = -0.38$ ,  $P < 0.05$ ) (Wolf and Kirschbaum 2002). In a more definitive study in which cognitive function was carefully assessed in 310 men (mean age 73 years), although no consistent association between total T and cognitive test scores was observed, men with higher bioavailable (loosely protein-bound) T concentrations had better cognitive test scores on the Mini-Mental State Examination (MMSE), Trails B and Digit Symbol ( $P < 0.001$ ) (Yaffe et al. 2002).



Data from Vermeulen et al. 1996

In a recently reported longitudinal study, Moffat and colleagues (2002) followed a subset of 407 men from the Baltimore Longitudinal Study of Aging (BLSA) who were 50-91 years old at baseline (mean age  $\pm$  SD = 64.1  $\pm$  9.4) for an average of 10 years, and performed repeated assessments of cognitive domains and morning T levels. They found that high free (but not total) T at baseline was associated with better scores on visual and verbal memory and visuospatial functioning, and moreover, predicted a slower rate of decline in visual memory. Similarly, hypogonadal men (defined by any free T value less than the 2.5<sup>th</sup> percentile for young adult men, n=149) scored lower on tests of visual and verbal memory and visuospatial functioning (rotation and scanning), and in addition, had an increased rate of decline in visual memory. Rate of change in T level did not appear to predict cognitive outcome.

Clinical trials have been done in which exogenous T or placebo were administered to elderly men, and cognitive measures carefully assessed over time. In a placebo-controlled T replacement study with 32 elderly hypogonadal men followed for one year, Sih and colleagues (1997) failed to demonstrate an effect of T on cognition. Kenny and colleagues (2002) randomised 67 hypogonadal men (mean age 76 years) to receive transdermal T patches or placebo patches for 1 year; 44 men completed the trial. Bioavailable T levels increased from 93  $\pm$  34 (SD) to 162  $\pm$  100 ng/dl ( $p < .002$ ) at 12 months in the testosterone group (n = 24) while no change occurred in the control group (n = 20). Scores on the Digit Symbol test improved in both the testosterone and placebo groups. Scores on Trailmaking B improved in men treated with testosterone ( $p < .005$ ), although the changes were not statistically different from the changes seen in the placebo group. Twelve-month scores on Trailmaking B for the entire group were correlated with 12-month testosterone levels ( $p = .016$ ).

Finally, in two clinical trials of testosterone in elderly men, hypogonadism was not an entry criterion. In one, Cherrier and colleagues (2001) randomized 25 elderly men to testosterone 100 mg/week or placebo for six weeks. Significant improvements in cognition were observed for spatial memory (recall of a walking route), spatial ability (block construction), and verbal memory (recall of a short story) in the testosterone group compared to the placebo group and compared to baseline. In the second, Janowsky and colleagues (1994) randomised 56 men (mean age 67 years) to receive T or placebo patches for 3 months. Compared to men who received placebo, men who received T had enhanced spatial cognition (especially visual perception and spatial construction processes), as measured by the Block Design subtest of the WAIS-R. Of note, the decrease in  $E_2$  level among men receiving T appeared to be a better predictor of

Block Design performance than the increase in T level. Other tested cognitive domains were not affected. This trial was limited by the relatively low T dose employed, and the limited sensitivity of the cognitive tests. Cumulatively, these data suggest that gonadal steroids may play a role in cognitive processing, and the area warrants further investigation.

#### Male depressive illness, HPG axis functioning and age

The psychiatric symptoms of hypogonadism overlap with symptoms of depression, and include low libido, fatigue, loss of confidence and irritability (Wang et al. 2000). Initial interest in this relationship has focused on MDD: first, on whether men with MDD had HPG abnormalities, and second on whether hypogonadal men developed a distinct 'secondary' MDD which might be reversible with T replacement. However, most studies that assessed this relationship have been methodologically flawed. Specific limitations include the following: 1) endocrinological studies of hypogonadal men have not included methodologically rigorous neuropsychiatric assessments; and 2) the few psychiatric studies in which HPG axis functioning was assessed in men with MDD have generally not used rigorous endocrinological methods, and have not focused on older men or on milder depressive syndromes. A second area of interest has been on population-based studies that assessed the association between measures of HPG axis function and depressive symptoms in older men.

Overall, in most clinical studies that have focused on neuroendocrine functioning and T replacement in men with MDD there is limited evidence that men with MDD—at any age—have significant HPG dysfunction, though evidence does support a blunting of early morning LH and T release (Schweiger et al. 1999; Rupprecht et al. 1988). Anecdotal reports and uncontrolled data suggest that in some men with hypogonadism, co-morbid MDD remits with T replacement (Rinieris et al. 1979; Heuser et al. 1999; Ehrenreich et al. 1999) or augmentation to partially effective antidepressant (Seidman and Rabkin 1998) and that in HIV-infected men with hypogonadism, T replacement is associated with improved mood, libido and energy (Rabkin et al. 2000; Grinspoon et al. 2000). It had been assumed that T replacement of hypogonadal men with MDD would conform to the 'hypothyroid' model, i.e. hormone axis normalization as an effective antidepressant. However, in a double-blind, randomised clinical trial of T replacement vs. placebo in 30 men with MDD and hypogonadism, we found that T replacement was indistinguishable from placebo in antidepressant efficacy (Seidman et al. 2001). More recent studies of T augmentation to antidepressant partial response have been more promising (Pope et al. 2003).

There are three large epidemiological studies in which both T level and depressive symptoms were assessed in middle-aged and elderly men: the Massachusetts Male Aging Study (MMAS) (Araujo et al. 1998), the Rancho Bernardo Study (RBS), (Barrett-Connor et al. 1999) and the ADAM questionnaire study (Morley et al. 2000). The MMAS was a population-based survey of 1,709 men aged 40-70 which included a morning T level and a self-report depression instrument, the Center for Epidemiologic Studies Depression Scale (CES-D). There was no correlation between CES-D-diagnosed 'depression' (using the standard cut-off of 16) and total T level (Odds Ratio 0.9, 95% CI= 0.75-1.1) (Araujo et al. 1998). The RBS was a population-based study of most adult residents of a southern California community (Barrett-Connor et al. 1999). In a 10-15 year follow-up study which included 82% of surviving community residents, 856 men aged 50-89 (mean 70 years, SD=9.2) completed the Beck Depression Inventory (BDI) and had a morning blood sample drawn for hormone assays. Free T level was inversely correlated with BDI score ( $B=-0.302$ , adjusted  $SE=0.11$ ,  $p=0.007$ ), signifying more depressive symptoms with lower free T levels. An important limitation to such cross-sectional correlational studies is that causality and clinical relevance are entirely unknown.

The ADAM questionnaire (Morley et al. 2000) was a forced yes or no 10-item symptom checklist for a presumed hypogonadal syndrome (termed 'androgen deficiency of the aging male'). In a validation study with 316 Canadian physicians, using a bioavailable T threshold for hypogonadism of 60 ng/dl, sensitivity was 88%, specificity 60%, and when administered on repeated occasions, it had a coefficient of variation of 11.5%. In the 21 hypogonadal men who subsequently received T replacement, mean ADAM score decreased from 5.8 to 2.1. Notably, the prevalence of hypogonadism increased steadily from 5% at age 40 to 70% at age 70. It appeared to the authors that the largest area of overlap, i.e. false positives, occurred in men with depression.

In further MMAS analyses we included a marker of androgen receptor (AR) function, the CAG repeat length. The AR gene has a polymorphic CAG repeat sequence encoding a variable-length glutamine chain in the N-terminal transactivation domain of the AR protein (Chamberlain et al. 1994). The length of the polymorphic CAG repeat is inversely correlated with the transactivation function of the AR, and inverse relationships have been described between the number of CAG triplets in the AR gene and the risk of prostate cancer, younger age at diagnosis, and poor response to endocrine therapy (Nelson and Witte 2002). We found that in middle-aged men there was a significant interaction between AR CAG repeats, T level, and

CES-D suggesting that these HPG state and trait features may interact to produce depressive symptoms. That is, whereas neither T level nor AR isotype alone were associated with CES-D-defined depression (i.e. CES-D  $\geq 16$ ), in a model using all three variables, AR isotype and T together predicted depression (significant effect for the interaction term) (Seidman et al. 2001a). Thus, this AR trait marker may define a vulnerable group in whom depression is expressed when T falls below a particular threshold.

Finally some clinical data suggest that the normative, age-related decline in T level, persisting over years, may lead to mild depressive illness, or dysthymia. In a clinical sample of elderly depressed men, we found that the median total T level in 32 men with dysthymia (295 ng/dl, range 180-520 ng/dl) was significantly lower than that of 13 age-matched men with MDD (425 ng/dl range 248-657 ng/dl) or 175 age-matched 'non-depressed' men (defined by CES-D $\leq 5$ ) from the MMAS sample (423 ng/dl, range 9-1021). Notably, among elderly dysthymic men, T level was in the hypogonadal range (i.e.  $\leq 300$  ng/dl) in 56.3% (Seidman et al. 2002). It is striking that in those with the most severe depressive symptoms, T levels were normal. This suggests that while dysthymia may phenomenologically overlap with hypogonadism, MDD does not.

### Conclusion

Delineation of the role of the HPG axis in the psychiatric problems of male aging may be of substantial public health importance. The sequelae of age-related female gonadal hypofunction (i.e. menopause) are well characterized and substantial: a growing body of evidence implicates reduced circulating oestrogen in the pathophysiology of mood disorders, neurodegenerative disorders, osteoporosis, cerebrovascular and cardiovascular diseases. Such knowledge has led to productive therapeutic research despite growing concerns about hormone replacement therapy. There is no parallel characterization of the psychophysiology of age-related male hypogonadism, despite important implications for the treatment of psychiatric problems in this population. Future research should focus on the possible CNS effects of mild, age-related HPG hypofunctioning, with emphasis on mild mood problems (e.g. dysthymia) and mild cognitive impairment.

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## Pharmacokinetic Interactions between Antiepileptic and Antidepressant Drugs

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### Summary

*The use of antiepileptic drugs (AEDs) for the treatment of psychiatric disorders has reached a new phase of clinical interest. They are commonly used in the therapy of psychoses, mood disorders, aggression and eating disorders. Pharmacotherapy combinations involving AEDs and antidepressant drugs are used to treat co-morbid psychiatric and neurological disorders, to reduce or control the adverse effects of a medication or to increase a medication effect. Therefore, the impact of pharmacokinetic interactions of this class of drugs is quite relevant. In this paper, the available data about the mechanisms of metabolic kinetic interactions between antidepressant and antiepileptic drugs, as well as their clinical significance, has been reviewed.*

**Key words:** antidepressant drugs, antiepileptic drugs, epilepsy, drug-interactions, pharmacokinetic.

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### Introduction

Antiepileptic drugs are widely used outside epilepsy as psychotropic agents and they are often used in combination with antidepressants in the treatment of schizoaffective and bipolar disorders. Generally, pharmacological interactions are classified as pharmacodynamic or pharmacokinetic. The former occur at the biologically active sites and the latter occur when one drug alters the disposition of another, resulting in a change in plasma or tissue drug concentration. Drug metabolism is a complex and important part of drug-kinetics and is mainly mediated by a complex inducible enzymatic system of hepatic cytochrome P450 mixed-function oxidases (CYP). Over 30 different human CYP enzymes have been identified, and detailed reviews about functions and nomenclature are now available (Nelson et al. 1996). Psychotropic drugs are mainly metabolised by four isoenzymes: CYP 1A2, 3A4, 2C and 2D6 (Nemeroff et al. 1996) (Table 1).

### Selective Serotonin Reuptake Inhibitors (SSRIs)

Data about interactions between *fluoxetine* and carbamazepine are contradictory (Grimsley et al. 1991; Spina et al. 1993; Gidal et al. 1993) but *in vitro* and *in vivo* data have demonstrated a moderate inhibitory activity on CYP2D6 and 3A4, probably mediated by the metabolites of fluoxetine, responsible for carbamazepine metabolism inhibition. In clinical studies, Andersen et al. (1991) demonstrated no interaction between *paroxetine* and carbamazepine, valproate or phenytoin. *Citalopram* demonstrated no clinically significant induction-inhibition properties, although drug inducers, such as carbamazepine, may enhance citalopram clearance (Leinonen et al. 1996). Although *fluvoxamine* is a potent enzymatic inhibitor of CYP1A2, Spina et al. (1993) demonstrated no significant changes in carbamazepine plasma levels.

*Sertraline* has enzyme inhibition properties on CYP2D6 and 2C but these are probably not clinically relevant, although there is the theoretical possibility of interaction with phenytoin (Haselberger et al. 1997; Rapeport et al. 1996a). Kaufman and Gerner (1998) reported two cases of lamotrigine-sertraline interaction, leading to high lamotrigine plasma levels, probably due to competitive inhibition of

lamotrigine glucuronidation, while Rapeport et al. (1996b) and Bonate et al. (2000) demonstrated the absence of drug interactions with carbamazepine and clonazepam, respectively.

Nelson et al. (2001) studied the inhibition properties of several SSRIs on phenytoin metabolism in an in-vitro study with human liver microsomes. The risk for a phenytoin-SSRI interaction has shown to be highest with fluoxetine and its metabolite, and less likely with the others (paroxetine and sertraline).

**Noradrenaline Reuptake Inhibitors, Noradrenaline Serotonin Reuptake Inhibitors and Noradrenaline and Selective Serotonin Antidepressants (NaRIs, NSRIs and NaSSA)**

No clinical studies are available about potential interactions of *venlafaxine* (NSRI) with AEDs. *Nefazodone* (NSRI) is a potent CYP3A4 inhibitor. Laroudie et al. (2000) investigated the presence of kinetic interactions between carbamazepine and nefazodone in 12 healthy subjects, observing a significant increase in carbamazepine AUC and a decrease in plasma level of nefazodone and its metabolites. This association should be carefully noted and carbamazepine plasma level monitoring may be useful in the clinical setting.

*Reboxetine* (NaRI) showed no evidence of any inhibition or induction properties of CYP enzymes, but there are no clinical studies available about potential interactions with AEDs. However, theoretically, modification in AEDs kinetic due to reboxetine is unlikely. On the other hand, drug inducers such as carbamazepine might increase reboxetine clearance.

Sitsen et al. (2001) demonstrated that *mirtazapine*

(NaSSA) has no effect on carbamazepine pharmacokinetic parameters. As for reboxetine, the dose of mirtazapine may have to be increased when used with inducers.

**Tricyclic Antidepressants (TCAs)**

Generally, phenobarbital, carbamazepine and phenytoin stimulate the metabolism of TCA (Perucca et al. 1985), while valproate is a metabolic inhibitor and can increase their plasma levels.

As far as *amitriptyline* and *nortriptyline* are concerned, their metabolism is significantly inhibited by valproate (Wong et al. 1996). Interestingly, carbamazepine affects not only the metabolism of *imipramine* and *desipramine* but also their protein binding leading to a significant increase in the free fraction (Szymura et al. 2001). Because of this phenomenon, a modification in imipramine dosage regimen does not seem to be necessary. As far as *clomipramine* is concerned, it has been demonstrated to cause a significant inhibition in carbamazepine metabolism in an animal model (Van Belle et al. 1995), while Fehr et al. (2000) reported an increase in serum clomipramine levels when co-prescribed with valproate.

**Atypical antidepressants and Monoamine Oxidase Inhibitors (MAOIs)**

Nawishy et al. (1981) investigated the presence of kinetic interactions between *mianserin* and three commonly prescribed anticonvulsants (phenytoin, carbamazepine and phenobarbital). All of them are inducers of the CYP450 enzyme system. They observed a significant reduction in mianserin plasma concentrations. Clinical studies of *trazodone*-AEDs interactions are lacking.

**Table 1**  
CYPs involved in anticonvulsant and antidepressant drugs metabolism

CYP1A2 Antidepressants	CYP3A4 Antidepressants	CYP2C9/10 Anticonvulsants	CYP2C19 Antidepressants	CYP2D6 Antidepressants
Amitriptyline	Amitriptyline	Phenytoin	Amitriptyline	Fluoxetine
Clomipramine	Clomipramine		Citalopram	Paroxetine
Imipramine	Desipramine		Clomipramine	Mianserine
Trazodone	Imipramine		Imipramine	Venlafaxine
Fluvoxamine	Norclomipramine		Moclobemide	Trazodone
	Nortriptyline			Nefazodone
	Trimipramine		<b>Anticonvulsants</b>	Amitriptyline
	Nefazodone		Mephenytoin	Clomipramine
	Sertraline		Esobarbital	Desipramine
	Venlafaxine		Mephobarbital	Imipramine
	<b>Anticonvulsants</b>			Norclomipramine
	Carbamazepine			Nortriptyline
				Trimipramine
				Maprotiline

**Table 2**  
Anticonvulsant and antidepressant drugs' activity on CYP450 enzyme system

Antidepressants	CYP1A2	CYP3A4	CYP2C9/10/19	CYP2D6
Fluoxetine		↓	↓	↓
Paroxetine				↓
Citalopram				
Sertraline		↓	↓	↓
Fluvoxamine	↓		↓	
Venlafaxine				
Reboxetine				
Amitriptyline				
Clomipramine				
Imipramine				
Moclobemide			↓	
Mianserine				
Trazodone				
Mirtazapine				
Nefazodone		↓		
<b>Anticonvulsants</b>				
Carbamazepine		↑		
Phenobarbital		↑		
Phenytoin	↑	↑		
Valproate				
Topiramate		↑	↓	

↑ induction; ↓ inhibition

The use of *bupropion* is limited because of the high seizure risk. Carbamazepine is a potent inducer of bupropion metabolism, leading the antidepressant plasma concentrations to undetectable levels. On the other hand bupropion has shown marked inhibition properties, increasing valproate levels (Popli et al. 1995) and probably also those of phenytoin (Tekle and al-Kamis 1990). Odishaw and Chen (2000) demonstrated no effect of steady state slow release bupropion on the pharmacokinetics of a single 100 mg lamotrigine dose, in a randomised, open label, cross-over study with twelve healthy subjects.

Ketter et al. (1995) investigated the safety and efficacy of *moclobemide* (MAOI)-carbamazepine cotherapy in a double-blind study. The combination was well tolerated with no modifications in the anticonvulsant's kinetics, but they did not assess moclobemide plasma concentrations.

**Conclusions**

Antidepressants are not equivalent in their potential for drug interactions when combined with AEDs (Table 2 and 3). Generally, valproate can be used more easily than carbamazepine, despite its plasma protein displacing and enzymatic inhibition properties. New anticonvulsants with better kinetic profiles (like gabapentin, topiramate, lamotrigine and levetiracetam) might be safely used in association with

**Table 3**  
Pharmacokinetic interactions between antiepileptic and antidepressant drugs

	CBZ	VPA	PHT	LTG	TPM	PB
<b>Fluoxetine</b>	=↑	↓	↑			
<b>Paroxetine</b>	=	=	=			
<b>Citalopram</b>	↓					
<b>Sertraline</b>	↓		↑=			
<b>Fluvoxamine</b>	=		↑			
<b>Venlafaxine</b>	=					
<b>Reboxetine</b>	↓					
<b>Amitriptyline</b>	↓	↑				
<b>Clomipramine</b>	↓	↑	↓			↓
<b>Imipramine</b>	↓*	↑	↓			↓
<b>Desipramine</b>	↓*	↑	↓			↓
<b>Nortriptyline</b>	↓	↑	↓			↓
<b>Moclobemide</b>	=					
<b>Mianserine</b>	↓		↓			↓
<b>Trazodone</b>			↑			
<b>Mirtazapine</b>	↓	=				
<b>Nefazodone</b>	↓	↑				
<b>Bupropione</b>	↓		↑		=	
<b>Viloxazine</b>		↑	↑	↑		

Symbols on the left refer to antidepressant drug and on the right to anticonvulsant drug, when prescribed in combination (in blank fields data are not available).

↑ increased plasma concentration, ↓ decreased plasma concentration, = unchanged plasma concentration

\* Dosage adjustments are not necessary

CBZ= carbamazepine, VPA=valproate, PHT=phenytoin, LTG=lamotrigine, TPM=topiramate, PB=phenobarbital

antidepressants, although it should be stated that topiramate induces CYP3A4 and inhibits CYP2C19. Older compounds, such as TCAs and MAOIs, have higher potential for interactions than newer ones, such as SSRIs or relatively novel agents, because of their selective effects on CYP enzymes.

Several factors must be considered when predicting the outcome of a potential interaction: patient-related (sex, age, ethnicity) and drug-related (the presence of active metabolites, the activity and potency at the enzyme site, the therapeutic window). In conclusion, all drugs (either anticonvulsants or antidepressants) should be slowly introduced, changing one drug at a time and trying to avoid overlapping, if possible. Careful clinical monitoring and appropriate adjustments in dosage and titration-time can usually lower the risk threshold of side effects due to pharmacokinetic interactions.

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## Serotonin Transporter Gene Polymorphism and Schizoid Personality Traits in Patients with Psychosis and Psychiatrically Well Subjects

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#### Summary

**Background and Objectives:** Serotonin transporter (5-HTT) gene allelic variants were shown to be associated with Neuroticism and Harm Avoidance but the results were not replicated in other studies. The current investigation was undertaken in a further attempt to study the relationship between 5-HTT polymorphism and personality traits.

**Subjects and Methods:** To evaluate a spectrum of personality traits, MMPI was administered to a sample including patients with affective disorders (n=114), patients with schizophrenia spectrum illnesses (n=110) and psychiatrically well controls (n=124). All groups were genotyped for VNTR-17 and functional insertion-deletion (5-HTTLPR) polymorphisms.

**Results:** An association was found between 5-HTTLPR polymorphism and scores on three MMPI scales: Psychopathic deviance, Paranoia and Schizophrenia in patients with affective disorders and Schizophrenia in normal subjects. Both affected and control individuals with 'ss' genotype exhibited lower scores on these scales.

**Conclusion:** We demonstrated that functional deletion/insertion allelic variation associated with decreased expression of serotonin transporter ('s' allele or 'ss' genotype) may restrict expression of schizoid traits in normal subjects and patients with affective disorders.

**Key words:** personality, serotonin transporter gene polymorphism, MMPI.

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#### Introduction

The relationship between personality traits and gene polymorphism has been a subject of interest during the past few years. The growing understanding that personality traits are repeatedly being shown to have heritable components prompted many investigators to concentrate their efforts on isolating particular personality variables seemed to be responsible for the heritable aspects of a risk for an illness (Bouchard 1994; Kendler et al. 1993; Alfimova et al. 1995). These findings were followed by reports of an association between personality traits and some polymorphic loci of candidate genes, namely, dopamine D4 receptor gene variants and novelty-seeking (Ebstein et al. 1996; Benjamin et al. 1996); s-allele of serotonin transporter (5-HTT) gene and anxiety (Lesch et al. 1996); tryptophan hydroxylase gene polymorphism and aggression (Manuck et al. 1998).

The 5-HTT gene proved to be one of the relevant candidate genes involved in the aetiopathogenesis of various psychiatric disorders. Two polymorphic variants within the gene, being currently used in association studies, have been so far described: (1) 17-bp variable tandem repeat (VNTR-17) located in the second intron with two common (with 10 or 12 repeats) and one rare allele (with 9 repeats) (Lesch et al. 1994) and (2) polymorphism in 5-HTT gene-linked polymorphic region (5-HTTLPR) located approximately 1 kb upstream of the transcription initiation site (Lesch et al. 1997). The latter polymorphism represented by long (l) and short (s) alleles has been reported to determine functional 5-HTT expression that might contribute to serotonin (5-HT) neurotransmission. Both polymorphisms are being intensively investigated for association with various psychiatric disorders (Stober et al. 1998; Schoeler et al. 1998; Ogilvie et al. 1996; Matsushita et al. 1997; Billet et al. 1997) and personality traits (Lesch et al. 1996; Ricketts et al. 1998; Ball et al. 1997). The most compelling evidence for 5HTT-polymorphism relating to personality features has been obtained in association studies between 5-HTTLPR polymorphism and anxiety-related traits, namely, Neuroticism on the NEO-Personality Inventory and Harm Avoidance on the Tridimensional Personality Questionnaire (TPQ) (Katsuragi et al. 1999; Ricketts et al. 1998; Murakami et al. 1999). However, the results have not been replicated in

other investigations (Jonsson et al. 1997; Jorm et al. 1998; Flory et al. 1999; Kumakiri et al. 1999; Nakamura et al. 1997; Ebstein et al. 1997; Gelenster et al. 1998; Ball et al. 1997). Nevertheless, the positive results encouraged the researchers to comment on a possible relationship between 5HTTLPR polymorphism and human behaviour. Based on the association between the 'ss' 5HTTLPR genotype and higher anxiety levels measured by the NEO-Personality Inventory and TPQ in normal individuals, Lesch et al. (1997) discussed the finding in the context of adaptation to social norms, assuming that persons who exhibited higher anxiety scores were inclined to conventional and socialized behaviour. Also, Nakamura et al. (1997) argued that the prevalence of an 's' allele in the Japanese population is a possible consequence of notable emotional restraint and interpersonal sensitivity to avoid criticism from the social group.

In the current study we attempted to confirm the hypothesis on the relationship between social adaptation and the 5HTTLPR 's' allele, using other self-rated questionnaire. We chose the Minnesota Multiphasic Personality Inventory (MMPI) because of its validity when administering to both normal and psychiatric populations (Butcher 1969; Gottesman and Shields 1972). Besides, MMPI scale scores have been earlier reported to correlate with serotonin levels in whole blood of psychiatric patients (Halevy et al. 1965; Castrogiovanni et al. 1992).

The investigation was carried out in three independent, approximately equal-sized samples represented by (1) patients with affective disorders, (2) patients with schizophrenia spectrum illnesses, (3) normal individuals. We used these samples assuming that trait personality characteristics are expressed higher after a disease manifestation and, therefore, appear to be more potential in searching for an association with genetic polymorphism.

## Methods and materials

### • Subjects

Patients were recruited from the clinical unit of the Mental Health Research Center, Moscow. All were inpatients who fulfilled ICD-10 criteria for schizophrenia (broad definition) and affective disorders. A diagnosis was based on the International Diagnostic Checklist for ICD-10 completed by a trained researcher as well as on medical records and clinical assessment by a psychiatrist. The total sample included 348 individuals. One hundred and fourteen subjects (35 male and 79 female; mean age 36.7 years, standard deviation (SD) 8.7 years; mean age at onset 29.4, SD 10.5 years) met the diagnosis of affective disorder (bipolar disorder (36 patients) and depression (78 patients)). One hundred ten patients (63 male and 47 female; mean age 25.3, SD 6.7 years, mean age at onset 23.7 years, SD 5.8 years) were

diagnosed as affected with schizophrenia and spectrum disorders (paranoid schizophrenia (48 patients), schizoaffective psychosis (42 patients), schizotypic disorders (9 patients) and schizophrenia with a less than two years illness duration (11 patients)). The control sample was recruited from staff and students and consisted of 124 psychiatrically well individuals (46 male and 78 female, mean age 31.6, SD 13.5 years) without a positive family history of psychiatric diseases. All subjects were ethnically Russian and from Moscow or the Moscow region community.

### • Personality assessment

To measure personality traits, the translated and adapted version of Minnesota Multiphasic Personality Inventory (MMPI) (Beresin et al. 1976) was administered to both patients and normal controls. MMPI (377 item version) comprises three validity scales (L, F, K) and ten basic clinical diagnostic scales: Hypochondriasis, Depression, Hysteria, Psychopathic deviate, Masculinity-Femininity, Paranoia, Psychasthenia, Schizophrenia, Hypomania and Social introversion. To reduce an influence of affected status on the personality trait evaluation, patients completed inventories after an improvement of their clinical state.

### • Genotyping and statistics

After obtaining informed consent from all subjects participating in the study, DNA was extracted from blood samples. Primers for genotyping of VNTR-17 and 5-HTTLPR loci and PCR performance were as described elsewhere (Lesch et al. 1994, 1996).

One-way ANOVA with Bonferroni correction as a *post hoc* test was applied to evaluate differences in mean trait scores between genotype subgroups.

## Results

Genotype distribution in the sample studied was in accordance to the Hardy-Weinberg equilibrium. MMPI scores for persons with different 5-HTT VNTR-17 genotypes revealed no significant differences on any scale in both control and affected groups. Significant differences between HTTLPR genotypes were obtained on the Psychopathic deviate ( $F=3.97$ ;  $p=.022$ ), the Paranoia ( $F=3.26$ ;  $p=.042$ ) and the Schizophrenia ( $F=4.25$ ;  $p=.017$ ) scales in the patients with affective disorders and on the Schizophrenia scale ( $F=3.49$ ;  $p=.034$ ) in the normal subjects (Table 1). In both samples, the individuals with the 'ss' genotype exhibited the lower scores on these scales. A trend towards the lower scores on the Psychopathic deviate ( $p=0.12$ ) and Paranoia scales ( $p=0.12$ ) was found in the control group, and on the Paranoia ( $p=0.07$ ) and Schizophrenia scales ( $p=0.14$ ) in the patients with schizophrenia spectrum disorders. The latter exhibited similar scores, regardless of genotype, on the

Psychopathic deviate scale. When the two groups of patients ( $n=224$ ) were combined, a significant between-genotype difference was obtained for the Paranoia scale ( $F=4.8$ ;  $p=0.01$ ) and a trend ( $p=0.058$ ) was observed for the Schizophrenia scale.

## Discussion

Thus, an association between 'ss' HTTLPR genotype and scores on three MMPI scales, namely Psychopathic deviate, Paranoia and Schizophrenia, was found in the patients with affective disorders. In normal individuals, the association was confirmed for the Schizophrenia scale, and the trend for association was observed for the Psychopathic deviate and Paranoia scales. In the patients with schizophrenia spectrum disorders, no statistically significant association between HTTLPR genotypes and MMPI scores was found, however, the trend for association was observed for the Paranoia and Schizophrenia scales.

Therefore, the 5HTTLPR polymorphism seems to be related to paranoid and schizoid traits. Genotype 'ss' might minimize expression of the traits, especially in the individuals without schizophrenic psychosis. The hypothesis is indirectly supported by that of Malhotra et al. (1998), who reported on an association between 'ss' genotype and lower intensity of hallucinations as well as lower total BPRS ratings for psychosis in a small sample of neuroleptic-free schizophrenic patients. However, given a high rate of false positive results in association studies, the correlation between schizoid traits and the HTTLPR polymorphism should be treated with caution until being replicated by other investigators. In contrast to the growing body of research examining a major effect of the HTTLPR polymorphism on susceptibility to

schizophrenia, there is so far a lack of reports on an association between this polymorphism and schizoid traits in nonschizophrenic populations.

In addition, the results could be discussed in the context of the above speculations on the relationship between social adaptation and 5HTTLPR polymorphism. As has been hypothesized earlier (Nakamura et al. 1997), the 's' allele is expected to prevent or constrain behaviour that could cause criticism from the social group. According to MMPI interpretation (Beresin et al. 1976), persons who exhibited higher scores on the Psychopathic deviate scale are characterized by a lack of conformity, lower impulse control, aggression and confrontation, and are inclined to conflicts. Higher scores on the Paranoia scale point to affective rigidity and hostility and those on the Schizophrenia scale reflect emotional withdrawal, strange thoughts and judgments, poor or selective social contacts. A personality profile distinguished by elevations on these scales reflect a particular behaviour. Of interest, an averaged MMPI profile of criminals who had committed murders was shown to have the highest profile peaks on Schizophrenia, Paranoia and Psychopathic deviate scales. Such a profile presumably reflected their low compatibility with other people, egocentricity and affective insensitivity in conjunction with a lower threshold for developing hostility and aggression (Sobchik 1998).

Lower scores on these scales indicate higher levels of socialization (right understanding of social norms), conformity and lack of spontaneity/ingenuity. Therefore, 'ss' genotype persons, who demonstrated the lower scores in the current study, appear to be more conventional and socialized.

**Table 1**

MMPI T-scores by 5HTTLPR genotype in the patients with schizophrenia spectrum disorders, affective disorders and normal subjects

Subjects	Patients with schizophrenia spectrum disorders			Patients with affective disorders			Normal subjects		
	ll n=42	ls n=46	ss n=22	ll n=44	ls n=53	ss n=17	ll n=45	ls n=57	ss n=22
5HTTLPR genotypes, MMPI scales									
Psychopathic deviate	57.2 13.6	57. 13.8	57.8 10.2	59.2 11.8	63. 13.2	53.3* 9.5	53.3 10.1	53.8 9.8	49.2 10.1
Paranoia	62.9 14.4	57.7 15.4	56.3 10.8	66.3 14.3	65.3 15.3	55.7** 9.7	54.7 11.	51.7 12.8	49.8 11.4
Schizophrenia	69.3 16.8	67.6 18.0	63.0 15.4	72.5 14.9	72.7 17.9	64.8*** 13.9	58.3 12.3	53.1 12.9	50.*** 14.1

Results are means  $\pm$ SD

ANOVA: Patients with affective disorders differ significantly by HTTLPR genotypes on Psychopathic deviate ( $*F=3.97$ ;  $p=.022$ ), Paranoia ( $**F=3.26$ ;  $p=.042$ ) and Schizophrenia ( $***F=4.25$ ;  $p=.017$ ) MMPI scales. Significant difference ( $****F=3.49$ ;  $p=.034$ ) was obtained for Schizophrenia scale in normal subjects.

However, using NEO-PI, Lesch and colleagues (1996) found an association between the 's' allele and higher scores on the Angry Hostility subscale of Neuroticism scale and lower scores on the Agreeableness subscale in male subjects, suggesting a more hostile and antagonistic personality in subjects with 's' allele. In contrast, in a sample of Caucasian males and females, Flory et al. (1999) demonstrated that Agreeableness scores were insignificantly higher in the carriers of the 's' allele, a finding compatible with that obtained in the present study. Given that serotonin is proposed to inhibit the impulses for engaging in aggressive and punished behaviours (for review see Lucki 1998), these results seem not to be counterintuitive.

It should be noted that an interpretation of the results is, to a certain extent, limited because the study failed to find a significant decrease in score values for all three scales and in all groups studied, which may be explained by insufficient sample size. When patients and controls were combined (n=348) and the sample power consequently increased, the by-genotype differences reached the significance level. In the statistical sense, it seems conventional, especially because an effect-size, being estimated as 0.3-0.5 for the groups of the patients, appears to be lower than might be expected for such psychologically different subjects. Nevertheless, we consider a pooling of patients and controls as incorrect, in a clinical sense.

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## A Double-Blind, Placebo-Controlled Trial of Clonazepam in Obsessive-Compulsive Disorder

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### Summary

Selective serotonin reuptake inhibitors (SSRIs) are currently the first-line pharmacological agents in treating obsessive-compulsive disorder (OCD). Appropriate treatment for OCD also involves cognitive behavioural therapy (CBT), including exposure and response prevention. As there is a time delay in seeing full therapeutic response, and not all patients tolerate SSRIs, there remains an unmet need for additional treatment approaches in OCD. In addition, most responders report only a partial reduction in symptoms. Clonazepam has demonstrated effectiveness in several preliminary reports in treating OCD. Twenty-seven patients with OCD were entered into a 10-week, double-blind, parallel design trial of clonazepam vs. placebo. Overall, only 3 out of 25 patients who had  $\geq 1$  rating on clonazepam/placebo were judged to be treatment responders, by scoring a 1 (very much improved) or 2 (much improved) on the CGI improvement scale. Responders included 2 of 9 in the placebo group and 1 of 16 in the clonazepam group. No significant difference was found between clonazepam and placebo groups on responder/non responder status ( $X^2 = 1.39$ ,  $df = 1, 24$ ,  $p = 0.238$ ), nor on change in YBOCS, HAM-A, HAM-D or NIMH scales from beginning to last evaluation carried forward. These findings suggest that clonazepam is not effective as monotherapy in treating OCD. Its effectiveness in specific subgroups of OCD patients with co-morbid anxiety disorders or as an augmentation strategy added to SSRIs remains to be determined.

**Key words:** clonazepam, benzodiazepine, serotonin, obsessive-compulsive disorder.

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### Introduction

Obsessive-compulsive disorder (OCD) is among the most common psychiatric disorders, with a prevalence rate of 1.91–3.31 % (Karno et al. 1988; Weissman et al. 1994). It is characterized by either obsessions and/or compulsions which are time consuming, cause marked distress or significantly interfere with the person's normal routine, functioning or relationships (American Psychiatric Association 1995). OCD is a chronic and disabling condition, often requiring long-term treatment.

Serotonin reuptake inhibitors (SRIs) are the first line treatment for OCD, with clomipramine, fluvoxamine, fluoxetine, sertraline and paroxetine having FDA approval for adults with OCD, and fluvoxamine and sertraline having FDA approval in child/adolescent OCD. Citalopram has an indication for treating OCD outside the US in several countries. However, a therapeutic lag of up to 12 weeks is often noted before seeing a full therapeutic response (Cartwright and Hollander 1998). Further, most responders report only a partial reduction in symptoms, not full remission. The selective serotonin reuptake inhibitors' (SSRIs) superior side effect profile compared with clomipramine, including less anticholinergic side effects, weight gain, potential cardiac conduction block and seizures, has made these drugs the treatment of choice. Not all patients, however, may be able to tolerate SSRIs' potential side effects, which include headaches, nausea, insomnia, sexual dysfunction and agitation. Therefore, the search for other agents or adjuvant medications for the treatment of OCD that are faster acting, have greater efficacy or are associated with less side effects continues.

Several uncontrolled reports suggested that clonazepam, a 7 nitro-benzodiazepine derivative, has substantial anti-obsessional properties in patients with OCD (Bodkin and White 1989; Bacher 1990; Hewlett et al. 1990; Ross and Piggott 1993; Leonard et al. 1994). Bodkin and White treated a 21-year-old man with OCD with clonazepam who at 0.5 mg t.i.d. had total remission of his compulsions and at 1 mg t.i.d. had complete remission of his obsessions and anxiety (Bodkin and White 1989). Bacher found clonazepam effective in treating a 60-year-old man with OCD, after other failed benzodiazepine trials (Bacher 1990). Hewlett and colleagues described three adult OCD patients

who responded successfully to clonazepam (Hewlett et al. 1990) and Ross and Piggott reported a 14-year-old adolescent boy with decreased obsessive thoughts after clonazepam alone (1 mg b.i.d.). In a controlled crossover study of 28 patients with OCD, subjects rotated through 6-week trials of clomipramine, clonazepam, clonidine and diphenhydramine (Hewlett et al. 1992). Both crossover and order effects were minimized by requiring OCD symptoms to return to baseline before each medication trial. Forty percent of the patients who had failed clomipramine treatment had clinically significant responses to clonazepam treatment, and clonazepam was significantly more effective than clomipramine during the first 3 weeks of treatment. There was also a unique cross-response found between clonazepam and clomipramine, such that 73% of the responders to clonazepam also responded to clomipramine, and 80% of the responders to clomipramine responded to clonazepam. Thus, the above studies suggest that clonazepam has some anti-obsessional properties both alone and in augmentation of SRIs.

Clonazepam's primary mode of action is to facilitate GABAergic transmission in the brain by a direct effect on benzodiazepine receptors. It differs from other benzodiazepines due to its effects on the serotonergic system, which could conceivably account for its putative anti-obsessional properties. An increase in the density of 5-HT<sub>1</sub> and 5-HT<sub>2</sub> binding sites in rat frontal cortex membranes following chronic in vivo administration of clonazepam was found, and upregulation was not seen with chronic diazepam administration (Wagner et al. 1986). In addition, clonazepam has been shown to not affect 5-HT synthesis (Hwang and Van Woert 1979; Pratt et al. 1979) and may decrease 5-HT utilization in the brain (Pratt et al. 1979). Clonazepam has shown efficacy in treating myoclonic syndromes that may be related to a cerebral deficiency of 5-HT (Chadwick et al. 1975; Chadwick et al. 1977) and its anti-myoclonic properties have been counteracted by the serotonin receptor blockers methysergide, metergoline and cinnanserin but potentiated by fluoxetine and chlorimipramine (Hwang and Van Woert 1979). The 5HT effects of clonazepam are of interest, since other benzodiazepines such as alprazolam have been shown to have no antiobsessional properties (Stein et al. 1992). As found in the above Hewlett study (Hewlett et al. 1992), there was a significant cross-response found between clonazepam and clomipramine such that patients responding to clomipramine also generally responded to clonazepam, suggesting a common mechanism. Given clonazepam's potential antiobsessional properties demonstrated in several preliminary reports as monotherapy, a controlled study to investigate its effectiveness as a sole treatment in OCD is needed.

This is the first randomised, double-blind, placebo-controlled parallel design trial of the safety and efficacy of clonazepam. It was conducted at three study centres consisting of the University of California San Diego, Mt. Sinai School of Medicine and Georgetown University School of Medicine.

### Methods

#### • Subjects

All subjects were outpatients recruited through physician referral. The years of recruitment were from 1993–1995. The screening phase-week 0 was used to evaluate potential patients for suitability into the study. Patients were drug free 2 weeks for all medications (except 4 weeks for fluoxetine) prior to entering the screening phase. The sample included both treatment naïve and treatment resistant patients with OCD. Treatment resistant patients were defined as individuals who have failed two or more trials with SRIs at adequate dose range for at least 12 weeks of therapy. Inclusion criteria for the study were the following: 1. DSM III-R diagnosis of OCD; 2. Age between 18 and 65; 3. Female patients of childbearing potential entered only if using medically acceptable birth control with negative pregnancy tests.

Exclusion criteria were the following: 1. DSM-III-R diagnoses of psychotic disorders (other than delusional disorder, somatic type), major depression with psychosis, bipolar I disorder or organic mental disorder; 2. Current substance abuse; 3. Current suicidal ideation; 4. Patients with major depression taking antidepressants and not in full remission for at least three months; 5. Pregnancy and/or breast feeding; 6. Use of depot neuroleptics or investigational drugs; 7. Intolerance to tapering or discontinuation of other medications; 8. History of major medical disorders such as current seizure disorder, cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine, haematologic or other systemic diseases.

Clinical diagnostic interviews were conducted by study psychiatrists who were experts in the OCD field. Patients who met the above criteria through diagnostic interview were evaluated by physical examination, routine laboratory tests and the following behavioural scales: Yale-Brown Obsessive-Compulsive Scale (YBOCS), NIMH Global Scale, Hamilton Depression and Anxiety Scales (HAM-D, HAM-A), and the Clinicians Global Impression of Severity Scale (CGI-S). A total of 27 patients were entered for study (11 at UCSD, 9 at Mount Sinai and 7 at Georgetown).

#### • Design and medication

The study was conducted in two phases: screening and baseline, and then a 10-week coded medication (clonazepam or placebo) phase. Patients were randomised in a skewed

fashion such that two-thirds of the patients were assigned to active (clonazepam) treatment and one-third of the patients were assigned to placebo. Medication was dispensed three times a day according to a pre-arranged dosage schedule (3-6 mg/day). Dosage levels were fixed during weeks 1-3 (1 mg at mid-day for week 1, 1 mg BID for week 2, and 1 mg TID for week 3) and flexible during weeks 4-10. In the event of intolerable side effects (sedation, hypersomnolence or ataxia), the dosage regimen was kept or reduced as needed. In the absence of significant side effects, dosage levels were increased beginning at week 4, not more frequently than every 7 days, to a maximum daily dosage of 6 mg/day. There was then a taper phase for all patients on clonazepam at the end of week 10 (or last evaluation done) at a rate of no greater than 1 mg/week. The primary outcome measure was the CGI-Improvement Scale. Rating scales were administered by study psychiatrists who were blind to treatment assignment. During weeks 1, 2, 4, 6, 8 and 10, YBOCS, NIMH Global, HAM-A, HAM-D, CGI Severity and Improvement scores were administered and vital signs, weight and adverse events recorded. A physical examination and lab tests were also included at week 10. Clinicians queried the patients at each visit regarding adverse events and these were recorded on an adverse events checklist. Side effects since last visit were recorded. The YBOCS assessed OCD symptomatology over the prior week.

#### • Analysis

Last observation carried forward analyses included all randomised subjects who completed at least one post treatment rating. Responders were defined as patients who rated very much improved (1) or much improved (2) on the CGI improvement scale at the last evaluation.

Comparison of outcomes based on CGI improvement between treatment and placebo groups was performed using chi-square analysis. In addition, independent samples t-tests were performed comparing mean change in YBOCS scores, HAM-D, HAM-A, and NIMH Global scores from beginning to last evaluation carried forward for patients treated with clonazepam and placebo. ANCOVA for mean change in YBOCS score between groups, covarying for baseline severity, was also conducted.

#### Results

Twenty-seven patients completed the screening phase and were entered into double-blind treatment of clonazepam or placebo. Two patients dropped out early in the study before week 2, including one from the clonazepam group and one from the placebo group, because of adverse events and were not included in the analysis. Eighteen patients received 10 weeks of study medication. Table 1 includes the number of patients entered, completed and dropped due to

lack of efficacy and adverse events. Side effects included complaints such as sedation, unsteady gait, dizziness and parasthesias of mild to moderate severity and were reported in 50% of the placebo group and 60% of the clonazepam group. Patient ages ranged from 23 to 57 years with a mean age  $\pm$  SD of  $37.9 \pm 10.1$ . In the study, 68 % of the patients were men and 32 % were women. Co-morbid diagnoses included social phobia (N=2), depression (N=1), body dysmorphic disorder (N=1), trichotillomania (N=1) and hypochondriasis (N=1).

**Table 1**

Treatment groups

Treatment Group	# Entered	# Completers	# Dropped (Total)	# Dropped (Adverse Event)	# Dropped (Lack of Effect)
Clonazepam	17	12	5	3 <sup>123</sup>	2 <sup>45</sup>
Placebo	10	6	4	2 <sup>67</sup>	2 <sup>89</sup>

<sup>1</sup> Week 0- AE

<sup>2</sup> Week 1- AE

<sup>3</sup> Week 2- AE

<sup>4</sup> Week 4- Lack of Effect/Moved

<sup>5</sup> Week 6- Lack of Effect

<sup>6</sup> Week 1- AE

<sup>7</sup> Week 2- AE

<sup>8</sup> Week 4- Lack of Effect

<sup>9</sup> Week 8- Lack of Effect

Three patients were unable to tolerate up to 3 mg daily of study medication and dropped out prior to week 3. Two other patients were not able to tolerate up to 3 mg daily in the fixed drug phase and continued on their dosages, with four additional patients having a reduction in dosage during the later flexible titration phase. The mean maximum drug dose for clonazepam patients was  $3.20 \pm 1.77$  for the intent-to-treat population and  $3.70 \pm 1.49$  for completers, and was  $2.33 \pm 1.06$  for placebo intent-to-treat patients and  $2.67 \pm 2.89$  for placebo completers. No significant difference between the groups was found. Of the 16 patients treated with clonazepam, one (6.25%) was a responder, and of the nine patients treated with placebo, two (22%) were responders. The responders were from two different sites, showing no apparent effect of response with particular site. The mean final CGI score was  $3.92 \pm 1.00$ . Thus, the responders included two patients on placebo and one on clonazepam, whereas the 22 non-responders included seven patients on placebo and 15 on clonazepam. There was no significant difference found between the two drug groups on the responder/non-responder status ( $X^2=1.39$ ,  $df=1$ ,  $24$ ,  $p=.238$ ). The two groups did not significantly differ in the proportion of treatment resistant patients.

No significant difference in improvement between clonazepam and placebo, comparing the change in YBOCS scores at the beginning and

last evaluation ( $t=.342$ ,  $df=1$ ,  $23$ ,  $p=.736$ ) was determined (Table 2). Of note, the mean YBOCS score  $\pm$  SD of the non-responders was  $25.5 \pm 5.40$  (range= 12-35) at the beginning of the trial and  $25.3 \pm 7.17$  (range= 8-40) at last observation, whereas the mean YBOCS scores of the responders was  $17.0 \pm 4.58$  (range= 12-21) at the beginning of trial and  $9.33 \pm 3.21$  at last observation (range= 7-13). This seems to indicate that the more severely ill patients did not respond at all and that a lower initial YBOCS score may have value in determining who may respond to the study medication. An analysis of covariance showed no significant difference for change on YBOCS between the two groups taking into account baseline severity ( $F=0.023$ ,  $df= 1,24$ ,  $p=0.882$ ). No significant differences were found between clonazepam and placebo comparing change on NIMH, HAM-D, and HAM-A scales from baseline to last evaluation carried forward (see Table 2).

**Table 2**

Baseline, endpoint and mean change scores of OCD patients receiving clonazepam or placebo

Rating Scales (mean $\pm$ SD)	Clonazepam N=16	Placebo N=9	Independent Samples T-Test
YBOCS Baseline	24.2 $\pm$ 5.4	25.3 $\pm$ 7.2	
Endpoint	22.6 $\pm$ 7.9	24.7 $\pm$ 10.0	
Mean change	1.7 $\pm$ 4.3	0.67 $\pm$ 5.1	$t=.342, df=1, 23, p=.736$
HAM-A Baseline	14.8 $\pm$ 8.0	14.7 $\pm$ 7.6	
Endpoint	13.8 $\pm$ 9.0	14.9 $\pm$ 9.8	
Mean change	1.1 $\pm$ 7.7	0.33 $\pm$ 9.8	$t=.394, df=1, 23, p=.697$
HAM-D Baseline	10.7 $\pm$ 7.3	11.7 $\pm$ 6.6	
Endpoint	11.1 $\pm$ 8.2	12.8 $\pm$ 8.3	
Mean change	0.44 $\pm$ 5.2	1.1 $\pm$ 8.1	$t=.256, df=1, 23, p=.801$
NIMH Baseline	8.3 $\pm$ 2.1	9.7 $\pm$ 2.2	
Endpoint	8.4 $\pm$ 2.5	9.7 $\pm$ 2.4	
Mean change	0.13 $\pm$ 2.4	0.0 $\pm$ 2.5	$t=.124, df=1, 23, p=.902$

#### Discussion

This is the first controlled parallel, double-blind study examining the efficacy of clonazepam versus placebo in OCD. These findings do not support the hypothesis that clonazepam is effective in the treatment of OCD as a monotherapy. Similar findings of lack of efficacy were found with another benzodiazepine, alprazolam, in an open-treatment study of 14 patients with OCD (Stein et al. 1992). This is in contrast to findings in other anxiety disorders, as clonazepam has been shown to be effective in treating social phobia (Davidson et al. 1993) and panic disorder (Davidson and Moroz 1998). This study does not evaluate whether clonazepam may have efficacy in OCD as an augmentation treatment, as has been previously reported (Leonard et al. 1994; Piggott et al. 1992). Leonard et al. (1994) reported a 16-year-old male

who had alleviation of OCD symptoms while taking clonazepam augmentation of fluoxetine (60 mg/day). Piggott and colleagues found that augmentation with clonazepam produced improvement in anxiety symptoms in a double-blind, placebo-controlled crossover augmentation study of 18 OCD patients who were taking either clomipramine or fluoxetine. Furthermore, it is conceivable that augmentation with clonazepam may benefit OCD patient subgroups with co-morbid anxiety disorders such as panic disorder, social phobia and generalized anxiety disorder, as was found in our study with the one clonazepam responder having co-morbid social phobia.

One limitation of the study includes a small sample size. Another potential limitation of the study was no a priori YBOCS cutoff for entry in the study. However, the baseline means and SD range for those on clonazepam ( $24.2 \pm 5.4$ ) and placebo ( $25.3 \pm 7.2$ ) are similar to other published trials at baseline. According to the low placebo response rate reported in OCD patients in previous controlled trials (Clomipramine Collaborative Study Group 1991), two-thirds of the patients in this study received clonazepam, and one-third received placebo. This is a potential methodological limitation, as in more recent studies there have been reports that the placebo response is rising (Montgomery et al. 1993; Ackerman and Greenland 2002). It is possible that the unbalanced active versus placebo arm (2:1 ratio) may have lead to a type II error. As mentioned earlier, rating scales were administered by study psychiatrists who were blind to treatment assignment but not to side effects. No independent evaluator blinded to side effects was utilized, which is a potential limitation. In addition, it is possible that fixed dosing during the study of up to 3 mg/day by week 3 may have accounted for adverse events such as sedation in some patients, masking clonazepam's anti-obsessional properties. The one clonazepam responder tolerated up to 5 mg/day without side effects. Therefore, it is possible that there would have been a response if other patients had tolerated this dose as only about one-third of patients were able to tolerate above 3 mg/day. Smaller doses of clonazepam (1-2 mg/day) have been reported to be an augmentation strategy in case reports of OCD, and controlled augmentation treatment trials are needed.

In conclusion, this negative study suggests that the benzodiazepine, clonazepam, does not appear to be effective alone in treating OCD. This negative finding is of importance to clinicians with respect to pharmacological treatment for this chronic and debilitating anxiety disorder.

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## Self-Rated Aggression Related to Serum Testosterone and Platelet MAO Activity in Female Patients with the Fibromyalgia Syndrome

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### Summary

To investigate self-rated aggression in relation to platelet MAO activity and serum testosterone in patients with fibromyalgia syndrome (FMS), we administered the Aggression Questionnaire – Revised Swedish Version (AQ-RSV) to 30 female patients with FMS. After correction for age, significant positive correlations were seen between serum testosterone concentrations and the AQ-RSV scores for Verbal Aggression ( $r=0.36$ ,  $p<0.05$ ) and Anger ( $r=0.37$ ,  $p<0.05$ ), whereas the platelet MAO activity was negatively correlated with the score for Verbal Aggression ( $r=-0.44$ ,  $p<0.05$ ). Our results suggest that aggression and irritability in female FMS patients might be increased by elevated testosterone concentrations in combination with reduced capacity of the serotonergic system as reflected by low platelet MAO activity.

**Key words:** aggression, platelet MAO activity, testosterone, fibromyalgia, female.

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### Introduction

Human research linking aggression and neurobiological factors has mainly been focused on psychiatric disorders characterized by depressed mood, suicidal behaviour, poor impulse control and diminished 5-HT neurotransmission in the central nervous system (Åsberg et al. 1976; Ågren 1983; Linnoila and Virkkunen 1992; Åsberg 1994). In animals as well as humans, serotonin seems to be the main transmitter system controlling aggression (Valzelli and Bernasconi 1979). There is a well-documented association between low concentrations of 5-HIAA in cerebrospinal fluid (CSF) and human aggression (Linnoila et al. 1983). As it has been suggested that the activity of monoamine oxidase (MAO) in platelets might reflect the capacity of the central serotonergic system (Oreland and Shaskan 1983), platelet MAO has been widely used as a peripheral marker of the 5-HT activity in the brain. These relationships are further strengthened by the positive correlations between the serotonin metabolite 5-HIAA in CSF and platelet MAO (Oreland et al. 1981; von Knorring et al. 1986).

Another neurobiological factor of importance for the generation of aggression is testosterone. In women, testosterone is not only produced by adrenal cortex, as in men, but also by the ovaries. Both animal and human studies show that androgens increase aggression (DeBold and Miczek 1985; Kalin 1999; Miczek 1987; Sundblad-Elvefors 1996; Moyer 1976; Van Goozen et al. 1995). The relationship between testosterone and aggression in women has been studied by testosterone administration to oophorectomized women (Sherwin and Gelfand 1985) and by analysis of psychotropic effects of anabolic steroids (Lukas 1993), among other methods. These and other studies suggest that testosterone increases aggression, which is further supported by the relationship between free testosterone and irrita-

bility/aggression in women with the premenstrual syndrome, PMS (Sundblad-Elvefors 1996).

A major obstacle in the study of human aggression has been the lack of adequate tools for 'measuring' and evaluating aggression. A number of observer- and self-rating instruments have been developed for research and clinical purposes. On the basis of the most commonly used self-rating aggression instrument, the Buss-Durkee Hostility Inventory (BDHI; Buss and Durkee 1957), Buss and Perry developed an Aggression Questionnaire (AQ; Buss and Perry 1992), which after adaptation to the Swedish population in 1999 is now known as the Aggression Questionnaire – Revised Swedish Version (AQ-RSV; Prochazka and Ågren 2001). The AQ-RSV standardization showed interesting differences in aggression and its sub-factors, not only with age and environmental factors but also with gender. The AQ-RSV is currently used in several studies that analyse relationships between human aggression and biological parameters in psychiatric disorders. Preliminary results in such a study in patients with treatment-refractory depression (Prochazka and Ågren Submitted) indicate involvement of gender-specific mechanisms in the relationship between aggression and neurobiological variables.

The fibromyalgia syndrome (FMS; Wolfe et al. 1995) is an intricate pain disorder that often involves depression, anxiety and stress. In recent years, exploration of the aetiology of the disorder has identified perturbation in the stress axes (Crofford et al. 1994; Pillemer et al. 1997; Griep et al. 1998) as well as low concentrations of serotonin and serotonin metabolites (Russell et al. 1992; Moldofsky 1992; Hrycaj et al. 1993).

Neurobiological and hormonal aspects of FMS have been studied by Anderberg, who has demonstrated that "hormonal state is of importance in the inter-connection with the monoaminergic systems, stress systems and pain processing systems" in women with FMS (Anderberg 1999). It may therefore be of special interest to investigate whether women with FMS differ from healthy women in aggression patterns, which in the present study are reflected by the neurobiological aggression markers MAO-B and testosterone.

The aims of the present study were to:

- analyse self-rated aggression and its subfactors in relation to the inherited serotonergic capacity, measured by the peripheral biological marker, platelet MAO-B, in women with FMS,
- analyse self-rated aggression and its subfactors in relation to the androgen hormone testosterone in women with FMS, and
- assess the impact of testosterone and platelet MAO-B on self-rated aggression in women with FMS.

## Materials and methods

### • Study design

We have previously investigated female FMS patients' aggression in relation to self-rated aggression in the general Swedish female population (Prochazka et al. In Preparation) as part of an extensive project investigating FMS and its relationships to stress, pain, neurobiological parameters and outcome of pharmacological treatment. All patients in the main study were consecutively recruited from the outpatient units of the Rheumatology and Rehabilitation Departments at the University Hospital in Uppsala, Sweden.

Following the pharmacological study, blood samples were collected for analysis of testosterone and platelet MAO activity. The patients were also offered treatment with a "new generation antidepressant", i.e. citalopram, fluoxetine, sertraline, paroxetine, mirtazapine or venlafaxin. The prescribed doses were within the range normally used for treatment of mild to moderate depressive illness. After one year, 40 patients consented to participate in further investigations, but ten of those patients dropped out due to different reasons.

### • Patients

Thirty female patients, 30-63 years (mean 50.2 ± 8.1 years), with FMS according to the American College of Rheumatology criteria (Wolfe et al. 1990), from whom blood samples and evaluable aggression inventories had been obtained, were included (Table 1). Mean duration of their FMS was 11.9 ± 7.0 years. Sixteen (53.3%) of the patients were in a postmenopausal status and nine (30.0%) were smokers. Patients with earlier severe heart disease or post myocardial infarction, post cerebral infarction, suicidal thoughts or severe depression were excluded from the study. At follow-up, the patients completed self-

**Table 1**  
Characteristics of female FMS patients

Variables	FMS patients (n = 30) Means ± SD
Age, years	50.2 ± 8.1
Postmenopausal status, n	16 (53.3%)
Smokers, n	9 (30.0%)
S-testosterone, nmol/L	0.78 ± 0.19
Platelet MAO activity*	13.8 ± 6.3
<b>AQ-RSV items:</b>	
• Global Aggression score	48.9 ± 10.0
• Physical Aggression score	13.4 ± 2.7
• Verbal Aggression score	10.0 ± 2.4
• Anger score	13.1 ± 3.1
• Hostility score	13.2 ± 4.4

\* 2 missing values

rating instruments focused on pain, well-being, depression, personality and aggression. Neurobiological parameters had been determined one year before the rating session. At the time of rating, 14 patients had treatment with an antidepressant drug (AD-T group) and 16 had used no anti-depressant medication for at least 3 months (No-T group). Since the AD-T and No-T groups did not differ significantly in age, serum testosterone, platelet MAO-B or self-rated aggression (Table 2), we found it reasonable to analyse the whole series as one. The fact that the AQ scores did not seem to be influenced by the AD treatment is somewhat unexpected but might indicate that rather stable personality traits are measured.

**Table 2**

Study variables compared in female FMS patients with (AD-T group) and without (N-T group) antidepressant treatment

Variables	AD-T group (n = 14) Means ± SD	N-T group (n = 16) Means ± SD	Statistical Diff AD-T/N-T group t test, p value
Age, years	50.0 ± 7.97	50.31 ± 8.40	t = 0.10, n.s.
S-testosterone, nmol/L	0.77 ± 0.11	0.79 ± 0.24	t = 0.27, n.s.
Platelet MAO activity*	13.49 ± 3.61	14.19 ± 8.30	t = 0.29, n.s.
<b>AQ-RSV items:</b>			
Global Aggression score	46.93 ± 8.36	50.63 ± 11.20	t = 1.01, n.s.
Physical Aggression score	12.43 ± 2.56	14.31 ± 2.52	t = 2.03, n.s.
Verbal Aggression score	9.79 ± 2.29	10.13 ± 2.55	t = 0.38, n.s.
Anger score	12.43 ± 3.10	13.69 ± 3.16	t = 1.10, n.s.
Hostility score	12.57 ± 3.93	13.75 ± 4.78	t = 0.73, n.s.

\* 2 missing values

### • Diagnostic and rating instruments Assessment of self-rated aggression

To assess aggression we used the AQ-RSV (Prochazka and Ågren 2001), which includes 29 randomly arranged items distributed into four scales measuring the aggression factors Hostility (8 items), Anger (7 items), Verbal Aggression (5 items) and Physical Aggression (9 items). Each item is rated on a 4-point scale, from least to most characteristic of the subject. The raw score for each of the four subscales is simply the total sum of these ratings.

Normative data for AQ-RSV have been obtained earlier from the general population (Prochazka and Ågren 2001). As compared to healthy volunteers, the women with fibromyalgia in the present study had somewhat higher scores regarding Physical Aggression and Hostility while the scores concerning Global Aggression, Verbal Aggression and Anger did not differ from those of women in the general population.

### Assessment of neurobiological aggression markers

The endogenous androgen hormone testos-

terone and a peripheral marker of 5-HT activity in the brain, the enzyme MAO-B, were selected as neurobiological aggression markers in this study. Both variables were found to be within limits for age-matched healthy women.

### Blood sampling procedures

To standardize the blood samples for all patients, the blood was drawn between 8.00 and 9.00 in the morning, after half-an-hour of rest. For the platelet MAO activity analysis, the whole blood was processed within 24 hours (see below). Blood for the analysis of testosterone was drawn into tubes and left untouched for 45 minutes before centrifugation at 3 500 rpm for 10 minutes. The blood plasma samples were stored in minisorbed tubes (NUNC, Denmark) and frozen to -70° before further processing and analysis of the hormones.

The blood sampling procedure was repeated after an interval of two weeks, and the calculations were based on the means of these two values. Platelet MAO activity at the first occasion was 12.46 ± 4.12 and at the second occasion 12.62 ± 4.29. The linear correlation between the two measurements was high,  $r=0.83$ ,  $p<0.001$ , and no significant mean difference was found ( $t=0.31$ , n.s.). Serum-testosterone was at the first occasion 0.78 ± 0.16 and at the second occasion 0.75 ± 0.10. The linear correlation between the two measurements was  $r=0.68$ ,  $p<0.001$ , without a significant mean difference ( $t=1.23$ , n.s.).

### Analysis of platelet MAO activity

Blood samples, approximately 5 ml, were drawn from the antecubital vein into Vacutainer® (Becton Dickinson, Franklin Lakes, NJ, USA) tubes containing ethylenediaminetetraacetic acid (EDTA) and platelet-rich plasma prepared by low speed centrifugation, 200 x  $\gamma$  for 10 minutes. Thereafter, platelet concentrations of the plasma samples were estimated electronically, and the plasma was stored at -80°C. Catalytic activity of platelet MAO was analysed by a radiometric assay with <sup>14</sup>C-labelled 2-phenyl-ethylamine ( $\beta$ -PEA) (New England Nuclear, Boston, MA, USA) as substrate, as previously described by Hallman and co-workers (Hallman et al. 1987). Briefly, 50  $\mu$ l of the sonicated plasma was added to 50  $\mu$ l of 0.1 mM <sup>14</sup>C- $\beta$ -PEA (0.5  $\mu$ Ci/ml) in 0.1 M sodium phosphate buffer (pH 7.8). The reaction mixture was incubated at 37°C for 4 minutes, and the reaction was terminated by acidification. Thereafter, the radioactive aldehyde/acid product was extracted into 750  $\mu$ l toluene and ethyl acetate (in volume 1:1) and subsequently quantified by scintillation analysis. Enzyme activity is expressed as nmol of substrate oxidized per 1010 platelets per minute. All samples were analysed blindly and in duplicate.

### Analysis of testosterone

Testosterone was quantified by solid-phase radioimmunoassay "Coat-A-Count total testos-

terone" from Diagnostic Products Corporation, Los Angeles, CA, USA. The total coefficient of variation (CV%) for the analysis of testosterone was 7.2% at 20.3 nmol/l.

• **Statistical analyses**

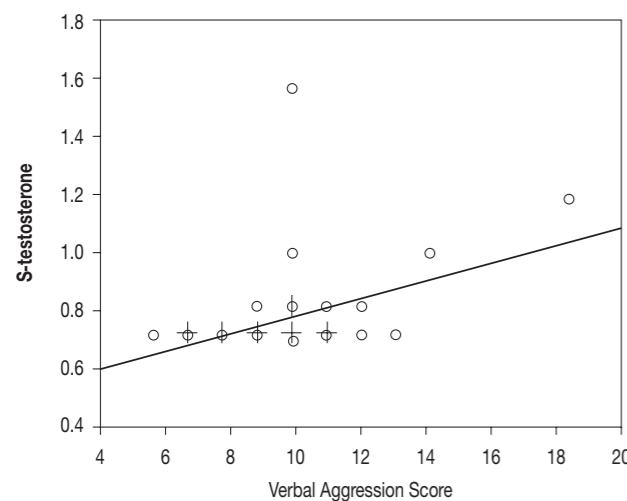
Descriptive statistics were calculated for the whole study population. Patients with and without antidepressant medication (AD-T and No-T groups) were compared by means of t-tests. Then, the relationships between the neurobiological markers, serum testosterone and platelet MAO activity, and the separate aggression variables were tested by means of Pearson's correlation coefficients. The effect of age on the correlations between the aggression variables and the neurobiological markers was sought by means of a series of linear regressions with age and the particular neuro-biological marker as the independent variable and the specific aggression variable as the dependent variable. All statistical analyses were calculated with SPSS Release 10.1 for MS Windows (Norusis 1990).

• **Ethical considerations**

The study was approved by the Research Ethics Committee at the Uppsala University and informed consent was obtained from the patients by means of the strict rules given by the Ethics Committee.

**Results**

Significant relationships between neurobiological aggression markers and self-rated aggression were found in the form of positive correlations between testosterone and the AQ-RSV scores for Verbal Aggression ( $r=0.39, p<0.05$ ) and Anger ( $r=0.39, p<0.05$ ). Verbal Aggression was also negatively correlated with the platelet MAO activity ( $r= -0.38, p<0.05$ ). (Table 3, Figures 1a,b).



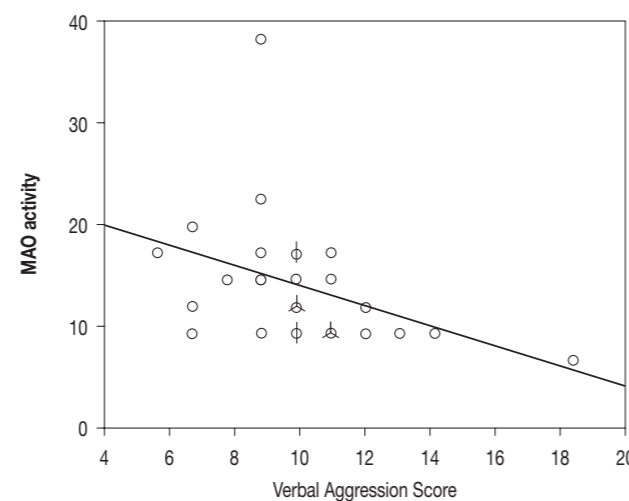
**Figure 1a**  
Serum testosterone interaction with AQ-RSV Verbal Aggression Score illustrated by linear regression lines.  $N=30$ , Verbal Aggression Score =  $0.48 + 0.03 \times$  S-testosterone,  $R^2 = 0.148$

As age is correlated with both the aggression variables and the neurobiological markers, a series of regression analyses were performed with the specific aggression variables as dependent and the specific neurobiological marker and age as independent variables (Table 4). Furthermore, as hormonal status and smoking habits could be confounding factors, these variables were also included in the regression analyses. Also, after correction for age, postmenopausal status and smoking habits, the positive correlations remained between serum concentrations of testosterone and Global Aggression and Anger, as did the negative correlation between Verbal Aggression and platelet MAO activity.

**Discussion**

The present study showed significant positive correlations between the neurobiological aggression marker serum testosterone and Global Aggression, Verbal Aggression and Anger, irrespective of age, postmenopausal status or smoking habits in women suffering from FMS. As expected, a significant negative correlation was found between platelet MAO activity and self-rated verbal aggression. Although there were no differences regarding age, levels in testosterone and platelet MAO activity, and self-rated aggression between the FMS patients subgroups (AD-T group and No-T group), the possibility that the anti-depressant treatment of 14 patients (AD-T group) might have influenced the results has to be taken into consideration.

Our results support previous observations of the role of androgens in disorders related to poor impulse control in women. A number of studies (Bäckström and Aakvaag 1981; Watts et al. 1985; Rubinow et al. 1988) have suggested that testosterone induces irritability and aggression-



**Figure 1b**  
Platelet MAO activity interaction with AQ-RSV Verbal Aggression Score illustrated by linear regression lines.  $N=30$ , Verbal Aggression Score =  $23.92 - 0.99 \times$  MAO activity,  $R^2 = 0.142$

**Table 3**

Pearson correlation coefficients between serum testosterone and platelet MAO activity, and the AQ-RSV aggression scores. Significant values are shown in boldface.

AQ-RSV Scores	S-testosterone	Platelet MAO activity
Global Aggression score	0.24, n.s.	0.04, n.s.
Physical Aggression score	0.13, n.s.	0.05, n.s.
Verbal Aggression score	<b>0.39, p&lt;0.05</b>	<b>-0.38, p&lt;0.05</b>
Anger score	<b>0.39, p&lt;0.05</b>	-0.26, n.s.
Hostility score	-0.01, n.s.	0.32, n.s.

related behaviour in women with premenstrual syndrome (PMS), but the correlations have not always been statistically significant. Supported by studies showing that the free serum testosterone fraction gives a clearer reflection of androgenicity in women (Jung-Hoffman et al. 1987), Eriksson and co-workers (1992) have demonstrated significantly elevated concentrations of free testosterone in PMS women with increased irritability/aggression.

The fact that the ovaries produce some of the female testosterone suggests that the menstrual cycle and differences between pre- and postmenopausal testosterone levels are likely to play a role in the interplay between testosterone and aggression. Waxman and McSherry Zatkis (1986)

**Table 4**

Relative effects of age, serum testosterone and platelet MAO activity on the AQ-RSV aggression variables estimated by means of a linear regression model with age and the specific neurobiological marker forced into the equation. Significant values are shown in boldface.

**4a.** Serum testosterone, age, smoking habits and postmenopausal status in relation to the aggression variables.

	Global Aggression Score	Physical Aggression Score	Verbal Aggression Score	Anger Score	Hostility Score
<b>S-Testosterone</b>					
Standardised $\beta$	0.43	0.24	0.40	0.56	0.25
t ; p	<b>2.09; p&lt;0.05</b>	1.10; n.s.	1.89; n.s.	<b>3.00; p&lt;0.01</b>	1.20; n.s.
<b>Age</b>					
Standardised $\beta$	-0.28	0.12	-0.23	0.08	-0.27
t ; p	1.14; n.s.	0.48; n.s.	0.89; n.s.	0.34; n.s.	1.10; n.s.
<b>Menopausal status</b>					
Standardised $\beta$	0.15	-0.39	0.04	-0.40	0.31
t ; p	0.60; n.s.	1.53; n.s.	0.16; n.s.	1.77; n.s.	1.27; n.s.
<b>Smoking</b>					
Standardised $\beta$	-0.41	-0.26	-0.07	-0.39	-0.50
t ; p	1.96; n.s.	1.21; n.s.	0.31; n.s.	<b>2.10; p&lt;0.05</b>	<b>2.41; p&lt;0.05</b>

**4b.** Platelet MAO activity, age, smoking habits and postmenopausal status in relation to the aggression variables. Significant values are shown in boldface.

	Global Aggression Score	Physical Aggression Score	Verbal Aggression Score	Anger Score	Hostility Score
<b>Platelet MAO activity</b>					
Standardised $\beta$	-0.10	0.06	-0.48	-0.33	0.19
t ; p	0.43; n.s.	0.27; n.s.	<b>2.34; p&lt;0.05</b>	1.64; n.s.	0.93; n.s.
<b>Age</b>					
Standardised $\beta$	-0.22	0.23	-0.38	-0.03	-0.09
t ; p	0.73; n.s.	0.78; n.s.	1.37; n.s.	0.11; n.s.	0.33; n.s.
<b>Menopausal status</b>					
Standardised $\beta$	0.06	-0.50	0.08	-0.37	0.17
t ; p	0.19; n.s.	1.79; n.s.	0.31; n.s.	1.40; n.s.	0.62; n.s.
<b>Smoking</b>					
Standardised $\beta$	-0.29	-0.16	-0.06	-0.25	-0.76
t ; p	1.35; n.s.	0.77; n.s.	-0.29; n.s.	1.28; n.s.	1.83; n.s.

reported an age of 42 years as an average onset of menopause in FMS women. Despite the fact that our study population included a wide age range of women (30 to 63 years), findings in our study were robust regardless of the menopausal status of the women. It is interesting to note, however, that Anderberg and co-workers (Anderberg et al. 1999) have reported that irritability and anxiety varied over the menstrual cycle in patients with FMS with as well as without PMS.

In contrast to testosterone, the platelet MAO activity is stable throughout life and under strong genetic influence with a heritability factor of about seventy five percent in both men and women (Pedersen 1993). A great number of clinical studies have shown significant correlations between low platelet MAO activity and personality characteristics such as impulsiveness, aggression, sensation seeking, psychopathy and type II alcoholism (von Knorring et al. 1984; Schalling et al. 1987; af Klintenberg et al. 1990). Hallman and co-workers (1987) have found that women suffering from PMS with irritability and depression as predominant symptoms had significantly lower platelet MAO activity and scored higher on self-rated personality inventories regarding temperamental correlates such as somatic anxiety, muscular tension and verbal aggression, as compared to healthy controls. Low platelet MAO activity has also been demonstrated in depressed patients with pain as a prominent symptom (von Knorring et al. 1984) and in patients with idiopathic pain syndromes (Almay et al. 1987).

There is strong evidence that platelet MAO activity might reflect the size/capacity or the turnover of the central serotonergic system (Oreland and Shaskan 1983; Damberg et al. 2001). As the serotonergic system is the main transmitter system controlling aggression and impulsivity in animals as well as humans (Valzelli 1974), it is reasonable to believe that the low platelet MAO activity is a marker for low serotonergic tone and, as a consequence, a decreased control over aggressive impulses in these women with FMS.

Our results indicate that irritability and aggression may be attributed to relatively high concentrations of testosterone in combination with disinhibited control due to diminished serotonergic capacity, as reflected by low platelet MAO activity. These findings agree with previously reported evidence for low serotonergic function in patients with FMS, as demonstrated by the finding that the selective serotonin reuptake inhibitor citalopram is more efficacious than placebo in women with FMS (Anderberg et al. 2000).

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## Quetiapine in the Treatment of Borderline Personality Disorder

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### Summary

*Affective dysregulation, impulsivity and cognitive-perceptual difficulties are the psychopathological nuclear dimensions of Borderline Personality Disorder (BPD). Psychopharmacological treatment may become necessary during episodes of acute decompensation in which suicidal or self-destructive behaviour erupts. Some classes of psychotropic drugs have demonstrated efficacy in diminishing symptom severity and optimising functioning, such as antidepressants, mood stabilizers, benzodiazepines, opiate antagonists and antipsychotics. Conventional antipsychotics are the best-studied psychotropic medications for BPD, but nonadherence is often due to their severe side effects. Preliminary data reveal efficacy of atypical antipsychotics in BPD. We describe the impact of the novel antipsychotic drug quetiapine on severe self-mutilation in two female patients with the diagnoses of BPD. In both cases, monotherapeutic treatment with quetiapine was well tolerated and resulted in a marked improvement of impulsive behaviour and, over time, overall level of function. Though promising, our findings have to be regarded as preliminary. Due to the overall paucity of data there is still insufficient evidence to make a strong recommendation concerning continuation and maintenance therapy with atypical antipsychotics in BPD. Thus, there is a clear need for further controlled studies to evaluate pharmacological treatment options for this disorder.*

**Key words:** *borderline personality disorder, psychopharmacology, quetiapine, impulsivity.*

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### Introduction

Borderline Personality Disorder (BPD) is characterized by a pervasive pattern of instability of interpersonal relationships, self-image and affects as well as a marked impulsivity (American Psychiatric Association 2000). Maladaptive personality traits and interpersonal reference styles are expected to be modified by psychotherapeutic approaches (Clarkin et al. 1999). However, the presence of suicidal, self-injurious and assaultive behaviour during episodes of acute decompensation make the use of psychotropic agents highly plausible. Pharmacological approaches to the treatment of borderline personality disorder are based upon evidence that disturbed neurotransmitter systems are implicated in the pathophysiology of the three psychopathological nuclear dimensions of cluster B personality disorders (i.e. affective dysregulation, impulsive-behavioural dyscontrol and cognitive-perceptual difficulties) (Siever and Davis 1991).

Several classes of psychotropic drugs have demonstrated efficacy in diminishing symptom severity and optimising functioning (Kapfhammer and Hipplius 1998). Selective Serotonin- and mixed Norepinephrine-Serotonin-Reuptake-Inhibitors and MAO-Inhibitors have been shown to be effective in treating the affective and impulsive-behavioural symptoms in borderline patients. Likewise, lithium carbonate, carbamazepine, divalproex and the novel anticonvulsant lamotrigine may be useful in some patients. Data concerning these agents in BPD are limited and routine precautions are necessary when using these agents. Benzodiazepines are used to alleviate feelings of tension and anxiety, but due to the frequent problems of drug abuse and dependence in borderline patients, tranquillisers should be used with caution. Very preliminary data from clinical case reports suggest opiate antagonists to reduce self-injurious behaviour by blocking mutilation-induced analgesia and euphoria (American Psychiatric Association 2001).

Antipsychotics, with efficacy for schizotypal and psychotic symptoms, anger and hostility are the best-studied psychotropic medications for BPD. Low-dose treatment with conventional antipsychotics (e. g. chlorpromazine, flupenthixol, thiothixene, haloperidol and trifluoperazine) have been shown to be superior to placebo. Despite a lack of published randomised controlled trials of atypical antipsychotics in BPD,

clinicians are increasingly using atypical agents for borderline patients. Preliminary data reveal efficacy of clozapine, olanzapine and risperidone in BPD (Chengappa et al. 1999; Khouzam and Donnelly 1997; Zanarini and Frankenburg 2001). To our knowledge, there are no published data on the efficacy of quetiapine in borderline personality disorder.

Quetiapine, a dibenzothiazepine derivative, is a novel antipsychotic agent with proven efficacy in the treatment of psychotic disorders (Kasper and Muller-Spahn 2000; Kasper et al. 2001). We report two cases of female patients with BPD in which monotherapeutic treatment with quetiapine led to a marked improvement of impulsive behaviour and overall level of function.

### Case reports

**Case 1:** A 22-year-old female student was admitted to our Department of General Psychiatry following her first suicide attempt by ingestion of various psychotropics. Since her early adolescence, she had suffered from recurring minor depressive episodes and parasuicidal ideations. Affective symptoms failed to respond to various psychotropic drugs. On the basis of a marked inconsistency in feelings and behaviour she had exhibited a promiscuous sexual behaviour and a lack of commitment to jobs or vocational trainings, and consecutively developed an impulsive-aggressive behaviour in terms of lacerating her arms and burning herself with cigarettes. Increasing social isolation followed. At admission, she was severely depressed. Psychotic features were not present. A treatment regimen with sertraline at a daily dose of 200 mg resulted in a pronounced alleviation of her depressive symptoms. At week 5, she had fully remitted from depressive symptoms and was discharged from hospital. She then regularly presented at her psychiatrist in private practice. However, while hospitalisation might have provided a temporal removal from external stress, her condition soon deteriorated after discharge. Though free from any suicidal ideations, several episodes of severe self-aggressive behaviour reoccurred. She was subsequently switched to quetiapine and received a final daily dose of 400 mg. Although she still reported feelings of chronic emptiness and anhedonia, the auto-aggressive impulses and gestures gradually ceased within the next few weeks. This led to a marked overall stabilization of her mental status. The patient has now been continuously treated with quetiapine (400mg/ day) as monotherapy for 6 months. No further self-mutilation occurred. Of note, she recently managed to turn over to a vocational training for medical massage.

**Case 2:** A 21-year-old female patient was referred to our Department of General Psychiatry owing to severe self-mutilation and an exacerbation of

psychotic symptoms. She gave a history of depressive episodes as well as brief psychotic episodes since the age of 17, but had never searched for psychopharmacological treatment. Rapidly oscillating between feelings of inferiority and superiority, her former history was characterized by dozens of job losses and interrupted educational pursuits. Severe difficulties in regulating negative emotions had led to numerous episodes of intentional self-injurious behaviour (i.e. cutting herself or banging her head against the wall). A broken relationship to her psychotherapist, with whom she had got sexually involved, finally preceded a further episode of parasuicidal behaviour and led to an exacerbation of psychotic symptoms, mainly in terms of paranoid delusions. At the time of referral to our department, she was in a stuporous state. She was treated with quetiapine up to a daily dose of 800 mg. Within 10 days, this regimen led to a complete remission of the psychotic symptoms. At time of discharge, she was in a stable condition. Given the efficacy and the good tolerability of this treatment regimen, quetiapine medication was proceeded at the same dose in the outpatient setting. During the eight months following initialisation of quetiapine monotherapy, neither psychotic episodes nor self-injurious behaviour have reoccurred, although her ability to enjoy hobbies or work is still poor due to her sensitivity to criticism or rejection. Fortunately, she managed to get a job as a receptionist in the hotel business, where she now works regularly.

### Discussion

Outpatient treatment of patients with BPD is usually difficult. Brief hospitalisation may become necessary during acutely stressful episodes or if self-destructive behaviour threatens to erupt. Moreover, the occurrence of psychotic episodes and parasuicidal behaviour often compromises psychotherapeutic efforts. Psychotherapy and psychopharmacotherapy may therefore interact positively, although this hypothesis has not been empirically validated.

Impulsivity is also regarded as a risk factor for suicidal behaviour, particularly in BPD (Soloff et al. 1994), thus management of impulsive, self-mutilating behaviour is a central goal of BPD treatment. Antipsychotics in general have been found to be effective in counteracting aggressivity and impulsivity. With regard to conventional antipsychotic agents, nonadherence is often due to conventional antipsychotics' side effects such as extrapyramidal symptoms (EPS) and endocrinologic symptoms, sedation and orthostatic dysregulation. Moreover, the risk of tardive dyskinesia must be considered in any decision to initiate long-term treatment with conventional neuroleptics. Open-label trials and case studies support the use of clozapine for patients with refractory psychotic symptoms or



severe self-mutilation behaviour in BPD patients, but the use of clozapine is limited because of its risk of agranulocytosis (Chengappa et al. 1999). In contrast, quetiapine has proven to have a more favourable tolerability. Due to its greater affinity for serotonin type 2A (5-HT<sub>2A</sub>)-receptors than to striatal dopamine (D<sub>2</sub>-) receptors, quetiapine is associated with a consistent placebo-level incidence of extrapyramidal symptoms and a lack of prolactin level elevations (Kapur et al. 2000; Kufferle et al. 1997).

As yet, quetiapine has been shown to be effective in reducing aggressive behaviour in schizoaffective disorder and behavioural disturbances associated with dementia (Citrome et al. 2001; Daniel 2000), but there are no reports on the anti-aggressive effect of quetiapine in BPD. We found quetiapine effective in terms of impulsivity and auto-aggression in two cases of severe BPD. Given the frequent problems in medicating BPD patients (e. g. non-compliance, demands for changes in dose or type of medication), quetiapine might be a particularly valuable treatment option due to its very low propensity to cause EPMS. Of interest, central serotonergic function has shown to be inversely related to aggression and suicidality (Herpertz et al. 1997; Simeon et al. 1992). The serotonergic mechanism of action of quetiapine may therefore be of additional benefit in treating impulsive (e. g. self-injurious) behaviour in BPD patients.

However, there still is insufficient evidence to make a strong recommendation concerning continuation and maintenance therapy with atypical antipsychotics in BPD. At present, this is best left to the clinician's judgment after carefully weighing the risks and benefits for the individual patient. Our findings with quetiapine are promising, but they have to be regarded as preliminary and certainly warrant replication in controlled clinical trials. Moreover, further research is needed to clarify whether certain subgroups of patients with BPD exhibiting particular symptom complexes (e. g. suspiciousness, anhedonia, affective lability, behavioural dyscontrol or impulsivity) may be preferentially responsive to a given medication.

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