REVIEW

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Personality Disorders

SABINE C. HERPERTZ[1], MARY ZANARINI[2], CHARLES S. SCHULZ[3], LARRY SIEVER[4], KLAUS LIEB[5], HANS-JÜRGEN MÖLLER[6] & WFSBP Task Force on Personality Disorders*

[1]*Department of Psychiatry and Psychotherapy, Rostock University, Rostock, Germany,* [2]*McLean Hospital, 115 Mill Street, Belmont, MA, USA,* [3]*Department of Psychiatry, University of Minnesota Medical School, MN, USA,* [4]*Mt. Sinai School of Medicine, Department of Psychiatry, Bronx VA Medical Center, NY, USA, and* [5]*Department of Psychiatry, Mainz University, Mainz, Germany,* [6]*Department of Psychiatry, Ludwig-Maximilians-University, Munich, Germany*

Abstract
These practical guidelines for the biological treatment of personality disorders in primary care settings were developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). They embody the results of a systematic review of all available clinical and scientific evidence pertaining to the biological treatment of three specific personality disorders, namely borderline, schizotypal and anxious/avoidant personality disorder in addition to some general recommendations for the whole field. The guidelines cover disease definition, classification, epidemiology, course and current knowledge on biological underpinnings, and provide a detailed overview on the state of the art of clinical management. They deal primarily with biological treatment (including antidepressants, neuroleptics, mood stabilizers and some further pharmacological agents) and discuss the relative significance of medication within the spectrum of treatment strategies that have been tested for patients with personality disorders, up to now. The recommendations should help the clinician to evaluate the efficacy spectrum of psychotropic drugs and therefore to select the drug best suited to the specific psychopathology of an individual patient diagnosed for a personality disorder.

Key words: *Borderline personality disorder, schizotypal personality disorder, anxious/avoidant personality disorder, evidence-based guidelines, biological treatment, pharmacotherapy, antidepressants, neuroleptics, mood stabilizer*

Correspondence: Sabine C. Herpertz, MD, Professor of Psychiatry, Department of Psychiatry and Psychotherapy, Rostock University, Gehlsheimer Str. 20, 18147 Rostock, Germany. Tel: +49 381 494 9500. Fax: +49 381 494 9502. E-mail: sabine-herpertz@med.uni-rostock.de

Contents

Executive summary of recommendations

Although personality disorders have high prevalence rates of approximately 10% in the general population and up to 40% among psychiatric patients, and although patients with these conditions are frequent users of psychiatric services, there is limited knowledge on evidence-based psychopharmacological treatments for these conditions. While specific recommendations will be provided for patients meeting the diagnostic criteria of borderline personality disorder (BPD), schizotypal (STPD) and anxious/avoidant (AVPD) personality disorders, there are hardly any trials of pharmacological interventions in any other type of personality disorder.

The data used for the development of these guidelines were extracted from all original articles published in peer-reviewed journals in English between 1980 (publication of DSM-III) and June 2007, as identified by a search in the Medline database with the main combinations pharmacotherapy *and* BPD, STPD or AVPD. Special emphasis was placed on randomized controlled trials that means, cross-over trials and open studies are only presented in case RCTs do not provide sufficient evidence for a particular level of recommendation.

In BPD, there are a limited number of randomized controlled trials (RCTs) of only moderate quality, with small sample sizes and short-term observation periods. No class of pharmacological agents appears to improve BPD psychopathology in general although the majority of studies have incorporated measurements of global functioning in addition to targeting special aspects of psychopathology. Medication suggestions will rather be given considering the dominating symptomatology of the individual patient. There is moderate evidence for the efficacy of atypical neuroleptics and second-generation antipsychotics on cognitive-perceptual symptoms and impulsive behavioural dyscontrol, including anger in personality disorders. These medications appear to work at lower doses than in schizophrenia. Selective serotonin reuptake inhibitors (SSRIs) are best shown to influence emotional dysregulation such as depressive mood, anxiety and mood swings and these effects appear to extend the improvement of comorbid conditions of mood and anxiety disorders. However, there is no evidence that SSRIs are effective for common symptoms such as emotional experiences of emptiness, loneliness, boredom or chronic dysphoria. In addition, there is no conclusive evidence that antidepressants reduce impulsive, aggressive or self-harming behaviours in BPD. SSRIs have shown a benefit for impulsive aggression in BPD patients with a comorbid condition of intermittent explosive disorder revised (IED); however, data from BPD samples without IED present inconsistent results. Although one study showed a superior effect of olanzapine monotherapy compared to fluoxetine alone on impulsive aggression, further studies are needed to test whether in the case of dominance of impulsivity and (auto)aggression, atypical neuroleptics may be recommended as first-line treatment. If not sufficiently helpful, mood stabilizers may be indicated such as divalproex sodium, topiramate, or lamotrigine, which have been shown to be effective for impulsive, aggressive behaviour in some controlled trials. However, sample sizes of studies on mood stabilizers are small in general and there is no data at all that indicates their efficacy in the long term.

In addition to an urgent necessity to conduct more controlled studies of good quality in BPD in general, more drug trials are warranted that focus on the improvement of affective instability. This domain of BPD psychopathology is not only known to be the most stable trait in BPD, but it has also been shown to be less changeable by psychotherapeutic interventions compared to impulsivity. Furthermore, effects of drugs on interpersonal relations in BPD patients have not been carefully examined, at all.

Because adherence to medication is not high in BPD, patients may be particularly vulnerable to even mild adverse effects. Correspondingly, classical neuroleptics are not indicated, all the more so as there is little evidence that classical neuroleptics reduce anxiety, depression, anger or improve global functioning in BPD. Finally, BPD individuals need safe drugs that have few risks in the case of overdose and parasuicidal gestures, meaning that irreversible MAOIs and lithium, despite some evidence of efficacy, are not likely to find broad application in BPD. No reliable comment can be provided on the length of pharmacological treatment, which may also vary as a function of the targeted domain of psychopathology. However, it may be recommended that a drug should be tried for at least 3 months with a sufficient baseline assessment of psychopathology, clearly defined targets of therapy and cessation of the drug if there is no benefit.

To conclude, no medication has been registered for personality disorders, and there is no evidence for a benefit of polypharmacy in these patients. Although there is some evidence for differential effects on psychopathology, classes of psychotropic agents act on a rather broad spectrum of symptoms and there is no database to suggest the combination of several drugs with respect to different targets. Patients with BPD should be informed that there is no strong evidence base for the prescription of any drug. However, the off-label use of psychotropic agents may help individuals with BPD to improve affective symptoms and impulsivity. A pharmacological treatment might also be indicated in severe conditions to support psychosocial interventions or even to make them possible although there is not much of an evidence-base on when/how to combine pharmacotherapy/psychotherapy. Since pharmacotherapy will be part of a multimodal treatment programme including individual and/or group psychotherapy, psychotherapeutic specialists on these disorders should usually be involved rather early on.

To date, very little research has been performed in STPD. There is some evidence for the benefit of atypical neuroleptics to patients with STPD and the comorbid condition of STPD and BPD.

Recommendations for pharmacological treatment of AVPD are limited in so far as the database is widely taken from RCTs that were conducted in (generalized) social phobia. However, there is good reason to extrapolate from data which is primarily related to anxiety disorders and not personality disorders data and to recommend an analogous procedure in the treatment of individuals with these highly related disorders. Apart from this shortcoming, there is broad evidence for the efficacy

of SSRIs and the SNRI venlafaxine, with side effects being small. According to experts' opinion medication should be taken for a minimum of 1 year. Irreversible MAO inhibitors have also been shown to be effective but due to safety aspects can only be recommended as an alternative in the case of non-response to first-line antidepressants and under the precondition that serious side effects are carefully checked. The probable effects of the anticonvulsant gabapentin and the GABA-analogue pregabalin need to be studied more intensively in the future.

Limitations

Pharmacological research in the field of personality disorders is still in its infancy and needs to be addressed much more intensively in the future. Studies in BPD are based on rather small samples of mostly outpatients and not on inpatients who have more current co-occurring disorders. Thus, the level of evidence is generally limited for inpatients. Furthermore, the recommendations of these practice guidelines are primarily based on randomized, controlled, double-blind trials, although open label trials have been included. When considering the data from open-label studies, one has to keep in mind the high placebo response rates pharmacological studies are especially prone to in samples with low symptom stability over time, i.e. borderline personality disorder. In addition, general limitations of controlled studies have to be considered, i.e. the exclusion of severely ill patients with a variety of co-morbid conditions and suicidality. This is a particularly significant handicap of pharmacological research carried out to date, since in the field of personality disorders, patients with several comorbid conditions and with latent or even acute suicidality are the principle rather than the exception. The vast majority of controlled pharmacological trials in BPD have been investigated over the short term, with some referring to an observation period of 6 months, but there is no evidence for a long-term effect. The necessity of long-term studies conflicts with high drop-out rates (up to more than 50%) in studies of BPD patients that cover more than 10 weeks of observation. Thus it may be difficult to obtain long-term data. Finally, there are only very few studies on add-on effects of medication to psychotherapy, although combination therapies reflect the common and widely accepted procedure in mental health services treating patients with personality disorders.

1. Personality disorders

1.1 Introduction

Personality disorders play a major role in today's psychiatric clinical practice. They are defined as enduring patterns of inner experience and behaviour causing distress and leading to maladaptive functioning in the areas of emotion, cognition, interpersonal relationships and impulse control. According to ICD-10, nine different diagnostic groups can be distinguished among the personality disorders, with some differences compared to DSM-IV (e.g., additionally incorporates schizotypal personality disorder on axis II). To date, pharmacological treatment strategies have only been studied in three personality disorders; therefore, specific recommendations will be restricted to borderline (BPD), schizotypal (STPD), and anxious/avoidant (AVPD) personality disorder.

Individuals with personality disorders not only use health services because of the inherent symptoms of this disorder, but they have an increased risk of suffering from further psychiatric disorders, particularly mood, anxiety and psychotropic abuse disorders. In addition, personality disorders play a role in the course of (chronic) somatic illnesses (including compliance problems and deficient development of coping mechanisms).

Epidemiological studies on the frequency of personality disorders in the general population point to prevalence rates between 6.7% (Lenzenweger et al. 1999) and 14.6% (Zimmermann and Coryell 1989). Among psychiatric patients, much higher prevalence rates between 40 and 60% are reported (Oldham et al. 1992). A large international study, which was initiated by the World Health Organization (Loranger et al. 1994), reported 39.5% of all psychiatric outpatients and inpatients to fulfil the diagnostic criteria of at least one personality disorder. The anxious/avoidant type was the most frequently diagnosed, i.e. in 15.2%. Recent data suggest that the follow-ups are better than expected. The Collaborative Longitudinal Personality Disorders Study (CLPS) indicates a short-term (1-year) diagnostic stability of personality disorders between 35 and 55%, and 44% on average (Shea et al. 2002). However, despite more changeability than expected on the diagnostic level, impairment in functioning appears to be rather enduring. After 2 years, the authors of the CLPS claim that rather stable, trait-like and attitudinal characteristics of personality disorders can be differentiated from more behavioural, reactive and highly changeable characteristics (McGlashan et al. 2005). The improvement in

psychosocial functioning is limited (Skodol et al. 2005) and the suicide risk is three times higher than in the general population, with a further increase in the case of comorbidity with mood or psychotropic abuse disorders (Stone et al. 1987). On the whole, individuals with personality disorders constitute a significant public health problem with extensive treatment utilization (Skodol et al. 2005). Personality disorders have long been regarded as highly stable conditions with little change under therapy. In addition, high diagnostic heterogeneity of samples due to the polythetic nature of the diagnostic categories, frequent variations in clinical phenomena and severity of illness over time, high comorbidity with axis I disorders again varying over time, high suicidality, difficulties in forming and maintaining a stable therapeutic alliance and finally the necessity of long-term outcome studies make it difficult to assess treatment efficacy and in particular, to perform controlled clinical trials. Consequently, data on psychopharmacological drug prescription in subjects with personality disorders published for German-speaking countries in 2005 suggest a symptom-driven, highly pragmatic and often not evidence-based use of psychotropic drugs in personality disorders (Heinze et al. 2005). The quality of treatment appears not to be significantly better in other countries (Bender et al. 2006).

Pharmacotherapy may target certain symptoms or aspects of a personality disorder, such as anxiety, emotional dysregulation or cognitive-perceptual symptoms. Therefore, randomized controlled trials (RCTs) have often reported outcome measures on a number of rather circumscribed symptoms and guidelines, e.g., those published for BPD by the APA (2001) have commented on different targets of pharmacotherapy. As clinicians are interested in the improvement of global functioning in patients with personality disorders, and as classes of psychotropic agents often act on a wide spectrum of symptoms, nosological approaches with a primary outcome measure have been favored recently, at least in the treatment of borderline and schizotypal personality disorder. This, however, does not mean that drugs exert effects on all aspects of the complex construct of personality disorders.

Contrary to the frequent use of psychiatric services, there is no drug licensed for personality disorders for this indication, up to now. Therefore, these guidelines on personality disorders only talk about 'off-label use'. In addition, quite a number of studies include only a small sample size in a trial. This means, that finding a significant result in an RCT with a small sample size rather indicates a strong effect while finding no effect can mean, that the trial was just underpowered (β-error problem).

This methodological problem implicating a higher risk for falsely negative than falsely positive results should be taken into consideration when interpreting the database in the field of personality disorders.

Since pharmacological research is almost absent for the majority of personality disorders, psychopharmacology may exclusively target comorbid conditions in all those personality disorders which in these guidelines are not reported in detail (i.e. those beside BPD, STPD, and AVPD). Here, medication is particularly indicated for the treatment of comorbid depressive and anxiety states, as they frequently occur in individuals with, e.g., narcissistic, histrionic and dependent personality disorders. SSRIs might have an advantage over TCAs in personality-disordered patients, as they have been argued to have an independent effect on symptoms of personality disorder (Reich et al. 2002). Regarding comorbidity with anxiety disorders, all currently available SSRIs as well as venlafaxine have been proven to be superior in the treatment of panic disorder and agoraphobia (Bakker et al. 2000). Venlafaxine and mirtazapine have shown efficacy in the case of frequently occurring mixed states of depression and anxiety (Rudolph et al. 1998; Fawcett and Barkin 1998). As medications can cause a transient worsening of anxiety symptoms, they should be started at low doses and then titrated slowly to the full therapeutic dose. Benzodiazepines are strongly discouraged in patients with personality disorders, as they can lead to sedation, cognitive and motor impairment, and may interact negatively with psychotherapy, in particular exposure techniques. In addition, paradoxical, disinhibitory effects have been reported (Cowdry and Gardner 1988). As personality disorders are chronic conditions, the risk of psychological and physical dependency may be higher than in episodic axis I disorders. It may be particularly high in subjects with borderline personality disorder who may abuse benzodiazepines in frequently occurring states of highly aversive tension. In substance-abuse disorders, anti-craving drugs may be indicated for personality-disordered patients in addition to psychotherapeutic interventions.

1.2 Goal and target audience of WFSBP guidelines

These WFSBP guidelines provide an update of contemporary knowledge of the borderline, schizotypal and anxious/avoidant personality disorders and evidence-based recommendations for their treatment. As psychotherapeutic treatment regimes have been found to be successful for borderline and anxious/avoidant personality disorder, the treatment of personality disorders should not be restricted to pharmacotherapy. These guidelines,

however, are primarily concerned with the biological, pharmacological treatment of patients. Psychotherapeutic treatment interventions are covered only briefly by providing reference literature for further evidence-based recommendations on psychotherapeutic treatments.

These guidelines were developed by the authors and arrived at by consensus with the WFSBP Task Force on Personality Disorders consisting of 23 international researchers and clinicians. The aim was to perform a systematic review of best available evidence pertaining to the treatment of these personality disorders and to bring about a summary of recommendations that are clinically and scientifically meaningful. Since the majority of RCT studies which have been performed in personality disorders do not fulfil the general WFSBP precondition of a sample size of at least 50 subjects, open trials are shortly presented, as well, at least for borderline and schizotypal personality disorder. These guidelines subsume the various opinions of respected experts and international representatives of the pharmacological state-of-the-art treatment of these disorders. These guidelines are intended for use in clinical practice for all physicians seeing and treating patients with personality disorders.

1.3 Methods of literature research and data extraction

The data used for the development of these guidelines were extracted from all original articles published in peer-reviewed journals in English between 1980 (publication of DSM-III) and June 2007, as identified by a search in the Medline database with the main combinations pharmacotherapy <u>and</u> 'borderline personality disorder', 'schizotypal personality disorder' and 'anxious' or 'avoidant personality disorder'. Additional searches for pharmacotherapy combined with one of the other DSM-IV personality disorders did not achieve any results. In addition, the following sources were used: American Psychiatric Association (2001) Practice Guideline for the Treatment of Patients with Borderline Personality Disorder; The Cochrane Database of Systematic Reviews (2006), Issue 1, Art. No.: CD005653, DOI: 10.1002/14561858.CD005653, Pharmacological Interventions for People with Borderline Personality Disorder; Work Group for Systematic Reviews and Metaanalyses in personality disorders at the University of Freiburg, Germany, in close cooperation with the Cochrane Collaboration (contact reviewer: K. Lieb); draft from the German Task Force for the development of Practice Guidelines for the Treatment of Patients with Personality Disorders. Special emphasis was placed on randomized controlled trials, which means cross-over

trials and open studies are only presented in the cases where RCTs do not provide sufficient evidence for a particular level of recommendation (compare Section 1.4). In addition, individual clinical experiences of the authors and members of the WFSBP Task Force on Personality Disorders were considered.

Only studies were included which primarily target the treatment of a specific personality disorder excluding those with mixed samples of personality disorders without differentiating the results and those which had been designed to test efficacy of drugs for axis I disorders with a comorbid PD. All studies considered were checked under methodological aspects; correspondingly only studies were considered that were based on ICD-10 or DSM-III/DSM-IV diagnostic criteria of BPD, applied valid measurements of diagnostics and change and included at least 10 subjects.

1.4 Evidence-based classification of recommendations

According to the WFSBP principle methodological approach of evidence-based medicine, four categories of evidence are used:

Level A. Good research-based evidence. This level is achieved if research-based evidence for efficacy is available from at least three moderately large (≥ 50 participants), positive, randomized controlled (double-blind) studies (RCT). At least one of these three studies must be a well-conducted, placebo-controlled study.

Level B. Fair research-based evidence. This level is achieved if research-based evidence for efficacy is available from at least two moderately large, positive, randomized, controlled (double-blind) studies (two comparator studies *or* one comparator-controlled and one placebo-controlled study) *or* from one moderately large randomized, controlled (double-blind) study (placebo-controlled or comparator-controlled) and ≥ 1 prospective, moderately large, open-label, naturalistic study.

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

Level D. Expert opinion-based (from authors and members of the WFSBPD Task Force on Personality

Disorders) supported by at least one prospective, open-label study/case series (≥ 10 participants).

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

1.5 Indications and goals of treatment for personality disorders

Individuals with personality disorders exhibit a continuum of psychopathology from mild up to severe levels of malfunctioning. They usually start their patient career with treatments related to volatile axis I disorders. The intermittent use of evidence-based (pharmacological or psychotherapeutic) treatments for axis I disorders (e.g., mood and anxiety disorders) is adequate for patients with a sufficient level of functioning in social life over wide periods of the disorder who show deterioration only in the face of particular stressors and challenges. A specific pharmacological treatment of the personality disorder or the typical pattern of multiple maladaptive behaviours and aversive inner experiences is indicated for patients with longer lasting deficiencies in social functioning, most of which have not improved sufficiently from a preceding purely psychotherapeutic approach. A specific pharmacological treatment is also indicated in severe conditions to support psychosocial interventions or even to make them possible. Pharmacotherapy should not always be assumed to be the treatment of choice for suicidality (Lieb et al. 2004) since there is no convincing evidence for the efficacy of medication in suicidal crises of personality-disordered subjects and since psychotherapeutic treatment programs are available that have been shown to reduce suicidal behaviour, e.g., in borderline personality disorder.

In the field of personality disorders treatments intend to improve the level of functioning such that explicitly predefined goals are achieved, or at best, the general (malfunctioning) criteria of a personality disorder are no longer fulfilled. This makes it necessary to exactly assess baseline psychopathology, to define target symptoms in addition to the improvement of global functioning, and to assess the effects of therapy along the predefined targets. There are hardly any data on the benefit of long-term treatment in personality disorders. Therefore, it is suggested that pharmacotherapy in personality disorders is usually indicated for a shorter or longer period of time and may be discontinued once patients have learnt to manage themselves and to make use of their strengths. From a clinical point of view, it may be recommended that a certain medication should be used for at least 3 months making a comprehensive evaluation of its effects possible.

Prior to treatment initiation, a stable and empathetic alliance between physician and patient should be established in order to reduce drop-outs from treatment. Furthermore, the choice of a medication should be the result of a process of patient-shared decision making. The patient should be clearly informed on the symptoms targeted by the drug, the proposed length of treatment and possible side effects. Medication should always be only a part of a comprehensive treatment plan including psychotherapy and social work, which should be developed based on the individual psychopathology, severity of illness and malfunctioning as well as history of former treatments. Treatment of personality-disordered patients in general should keep a balance between support and the patient's responsibility to actively engage in problem solving.

2 Borderline personality disorder

2.1 Diagnosis, epidemiology, aetiology, and course of borderline personality disorder

Borderline personality disorder (BPD) is by far the best investigated personality disorder regarding aetiology and treatment. It has a major impact on health services, particularly in the frequently occurring situations of crisis, and therefore causes a considerable amount of direct costs. The ICD-10 refers to the diagnostic category of Emotionally Unstable Personality Disorder with an Impulsive and a Borderline subtype. The Borderline subtype is similar to the BPD DSM-IV definition, which consists of nine criteria, with the definite diagnosis requiring that five of these be met in addition to the general criteria of PD (see Table I).

The dominating and best discriminating features of borderline psychopathology can be described by four facets of psychopathological symptoms: affective disturbance, impulsivity, disturbed cognition, and intense unstable relationships (Zanarini et al. 1990a; Lieb et al. 2004).

Affective disturbance in BPD is characterized by dysphoric affect, usually experienced as aversive tension, including qualitatively rather diffuse feelings of rage, fear, sorrow, shame, guilt and inner emptiness. Patients exhibit intense mood reactivity in the interpersonal realm, with frequently and rapidly changing affective states within 1 day. Impulsivity is reflected in different modes of more or less severe self-harm, self-injurious and suicidal behaviour, in particular, but also as disordered eating, substance abuse, reckless driving, wasting money, etc. Aggressive behaviour against others may also occur, with

Table I. Classification and criteria according to DSM-IV (Borderline Personality Disorder) and ICD-10 (Borderline Type of Emotionally Unstable Personality Disorder).

ICD-10 (Research criteria)	DSM IV

F60.3 Emotionally unstable personality disorder
F60.30 Impulsive type
A. The general criteria of personality disorder (F60) must be met.
B. At least three of the following must be present, one of which is (2):
  1. A marked tendency to act unexpectedly and without consideration of the consequences.
  2. A marked tendency to quarrelsome behaviour and to conflicts with others, especially when impulsive acts are thwarted or criticized.
  3. Liability to outbursts of anger or violence, with inability to control the resulting behavioural explosions.
  4. Difficulty in maintaining any course of action that offers no immediate reward.
  5. Unstable and capricious mood.
 	
F60.31 Borderline type
A. The general criteria of personality disorder (F60) must be met.
B. At least three of the symptoms mentioned above in criterion B (F60.30) must be present, and in addition at least two of the following:
  6. Disturbances in and uncertainty about self-image, aims and internal preferences (including sexual).
  7. Liability to become involved in intense and unstable relationships, often leading to emotional crises.
  8. Excessive efforts to avoid abandonment.
  9. Recurrent threats or acts of self-harm.
  10. Chronic feelings of emptiness.
	A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
	  1. Frantic efforts to avoid real or imagined abandonment. (Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5).
	  2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
	  3. Identity disturbance-markedly and persistently unstable self-image or sense of self.
	  4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5)
	  5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour.
	  6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
	  7. Chronic feelings of emptiness.
	  8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
	  9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

BPD being one of the most frequent personality disorders in forensic settings (Coid et al. 1992). Manifestations of disturbed cognition are mostly non-psychotic and appear as overvalued ideas of being bad, as dissociative experiences of depersonalization, derealization and pseudohallucinations (i.e. patients recognize the delusional nature) (Zanarini et al. 1990b). However, delusions and hallucinations may also occur, typically of transitory, circumscribed nature, often related to former traumatic experiences and usually occurring in the context of affective derangement (therefore called quasi-psychotic symptoms). Relationships are dominated by a profound fear of abandonment and by unpredictable changes between idealization and longing for closeness at one time and arguments and sudden break-ups at another.

Prevalence rates reported from field studies range between 0.7% in Norway and 1–8% in the USA. Among psychiatric inpatients, BPD is diagnosed in up to 20% of patients and it is predominantly diagnosed in females (about 75%). However, general-population-based studies show no clear gender difference. First symptoms of BPD usually start in early adolescence, although the prevalence of PDs decreases significantly between early adolescence and early adulthood (Johnson et al. 2000). BPD has a better prognosis than other serious mental illnesses such as schizophrenia or bipolar disorder. In two prospective studies (Zanarini et al. 2003; Grilo et al. 2004) in 290 and 154 patients diagnosed with BPD, only about 65% fulfilled diagnostic criteria of BPD after 2 years. Zanarini et al. (2003, 2006) followed patients for 10 years and reported BPD diagnosis to be still present in only 32% after 4 years, 25% after 6 years, and 12% after 10 years. Relapse rates were low, with 6% of those who had achieved remission within 6 years relapsing, and 4% committing suicide. Forty percent of the patients who eventually remitted experienced their first remission in the first 2 years of follow-up. Despite a rather favourable course with regard to remission rates of the full-blown disorder, BPD individuals suffer from a significant level of symptoms, particularly affective instability in the long term. In addition, suicide attempts are very common among BPD patients, and among those who committed suicide, 40–65% met criteria of a personality disorder, with BPD being the most common (Welch and Linehan 2000).

BPD patients show high comorbidity with axis I and axis II disorders (Zanarini et al. 2004 a,b). Among axis I comorbidity, the highest prevalence rates are found for major depression, dysthymia, bipolar disorder, substance abuse disorders, post-traumatic stress disorder, social phobia, and eating disorders, while in terms of axis II disorders, avoidant, dependent, and paranoid personality disorders are most frequently diagnosed.

Causal factors are only partly known, but it is sure, that there are both genetic and adverse psychosocial factors, that contribute to the development of BPD. While physical and sexual abuse are known to be frequent psychosocial stressors in childhood, neurobiological research has found differences in the volume and function of brain structures related to affect regulation and impulsivity, e.g., amygdala, hippocampus, parts of the prefrontal cortex compared to healthy controls. Functional neuroimaging data rather consistently point to amygdalar hyperreagibility which may act in concert with a deficient prefrontal top-down control, located in ventromedial parts of the prefrontal cortex and the anterior cingulate cortex. Serotonergic dysfunction in the prefrontal cortex including the anterior cingulate cortex appears to contribute to impulsivity and impulsive aggression.

BPD individuals are frequent users of inpatient and outpatient psychiatric services, as data from the USA suggest (for review, see Lieb et al. 2004). Over the lifetime, 97% of patients seeking help receive outpatient care from an average of six therapists, 37% receive day treatment and 72% undergo psychiatric hospitalizations. In Germany, the annual rehospitalization rate amounts to 80% of the total group (cf. German Treatment Guidelines). A study on the long-term course throughout 6 years of prospective follow-up in BPD indicated high rates of intensive polypharmacy, with 40% of the patients taking three or more medications concurrently, 20% four or more and 10% five or more (Zanarini et al. 2003). Treatment practice in BPD has been criticized for being simply derived from medications in axis I disorders, which show more or less similarities in terms of symptoms. Up to now, there has been no effort to develop more specific drugs for BPD, focusing for instance on affective instability, low stress tolerance, dissociation, rejection sensitivity etc.

APA practice guidelines published in 2001 for the treatment of BPD recommend a symptom-targeted approach (APA 2001). Based on a comprehensive review of evidence-based and 'best practice' treatment strategies in BPD, psychotherapy was designated as the primary treatment, with pharmacotherapy recommended as an adjunctive, symptom-targeted component of treatment. Specific algorithms were developed which were related to three main symptom clusters of BPD: cognitive-perceptual symptoms, affective disturbance, and impulsive-behavioural dyscontrol. Low-dose neuroleptics were recommended as first-line treatment for cognitive-perceptual symptoms. For affective disturbance, SSRIs or related antidepressants were recommended, with switch to a second SSRI or other antidepressant in the case of non-response. SSRIs were also reported as the first-line treatment for impulsive-behavioural dyscontrol followed by a change to or adding a low-dose neuroleptic if treatment response is not sufficient. Typical medication practices have since been published in the US for BPD patients, which indicate only a low correspondence with the guidelines at a point in time when the guidelines were not yet published (Oldham et al. 2004). Prescription of SSRIs appeared to be related more to comorbid conditions of major depression than to the prominence of affective disturbance symptoms or behavioural dyscontrol in BPD psychopathology. Impulsive-behavioural dyscontrol predicted the use of neuroleptics rather than cognitive perceptual symptoms. In addition, a prominent feature of impulsive behaviour was significantly correlated with a treatment with anticonvulsants. These data again revive the controversial discussion of whether a symptom-targeted approach is sufficiently evidence-based or may favour the practice of polypharmacy frequently observed in BPD. Therefore, the following review comprises the presentation of the treatment potency of different classes of pharmacological agents on both general psychopathology and differential symptoms. The recommendations should help to evaluate the efficacy spectrum of psychotropic drugs and therefore to select the drug best suited to the specific psychopathology of an individual BPD patient.

2.2 Treatment with antidepressants (cf. Table II)

2.2.1 Classification and efficacy. Affective disturbance and mood reactivity as two of the most prominent features of BPD suggest the application of antidepressants. Since impulsivity has repeatedly been shown to be associated with low prefrontal serotonergic transmission in BPD and other impulsive personality disorders, antidepressants with a serotonergic mechanism have also been used with the aim of decreasing impulsive behaviours. Indeed, antidepressants have been the most frequently studied class of psychotropic agents in BPD in RCTs, with dosages tested within the middle range.

The following antidepressant groups have been tested in BPD: tricyclic antidepressants (TCAs),

Table II. Randomized controlled trials on antidepressants in borderline personality disorder.

Authors/Journal	Subjects	Study design	Agent/Dose	Results
Montgomery & Montgomery (1982, 1983) J Affect Disord, Br J Clin Pharmacol	Patients with multiple episodes of suicidal behaviour $N = 58$ (thereof $N = 30$ with BPD)	RCT for 6 months	Mianserine *vs.* placebo	no better effect on reduction of suicidal behaviour than placebo
Cowdry & Gardner (1988) Arch Gen Psychiatry	BPD $N = 16$ ♀ No current major depression	Randomized crossover-trial; after first phase 1 week of tapering off + 1 medication-free week; each trial for 6 weeks	1. phase: placebo *vs.* alprazolam *vs.* carbamazepine 2. phase: trifluoperazine *vs.* tranylcypromine (irrev. MAOI)	Significant overall improvement reported by physicians on tranylcypromine and carbamazepine, reported by patients only on tranylcypromine; decrease of behavioural dyscontrol on carbamazepine, increase on alprazolam
Soloff et al. (1989) J Clin Psychopharmacol	BPD $N = 90$ no bipolar disorder	RCT for 5 weeks Comparator: Haloperidol (4–16 mg)	Amitriptyline (TCA) 100–175 mg vs Haloperidol (4–16 mg)	Significant improvement of global depression and hostile depression low drop-outs
Soloff et al. resp. Cornelius et al. (1993) Arch Gen Psychiatry, Am J Psychiatry	BPD $N = 108$ in acute phase, $N = 54$ in continuation phase Comorbid depression included	RCT for 5 weeks, followed by 16 weeks of continuation therapy Comparator: Haloperidol (1–6 mg)	Phenelzine (irrev. MAOI) 15–90 mg vs. haloperidol	Phenelzine better than placebo and haloperidol on depression, anxiety, anger, hostility, very modest effect in continuation period on irritability and depression moderate drop-outs in the whole group
Salzmann et al. (1995) J Clin Psychopharmacol	BPD $N = 22$ mild to moderate severity (no SIB), no axis I comorbidity	RCT for 13 weeks	Fluoxetine (SSRI) 20–60 mg vs. placebo	Significant improvement of anger, anxiety and depression moderate drop-outs in the whole group
Coccaro u. Kavoussi (1997) Arch Gen Psychiatry	PDs with impulsive, aggressive behaviour $N = 40$ 33% with BPD	RCT for 12 weeks	Fluoxetine (SSRI) 20–60 mg/day vs. placebo	Significant decrement of manifest verbal and impulsive aggression and irritability, no influence on self-perception of aggression, improvement of global functioning high drop-outs in the fluoxetine and in the placebo group
Rinne et al. (2002) Am J Psychiatry	BPD $N = 38$ females moderate to severe severity most with unipolar mood and anxiety disorders exclusion of bipolar disorder	RCT for 6 weeks 'half cross-over' for 6 weeks, open 'follow-up' for 12 weeks	Fluvoxamine (SSRI) 150–250 mg/day vs. placebo	Significant decrement of rapid mood shifts, but no influence on aggression and impulsivity low drop-outs
Simpson et al. (2004) J Clin Psychiatry	BPD $N = 25$ females exclusion of bipolar disorder	RCT for 10 to 11 weeks DBT + Fluoxetine vs. DBT + placebo	Fluoxetine (SSRI) 40 mg/d vs. placebo	Data from $N = 20$ completers: no additional benefits from adding fluoxetine to DBT on measurements of global functioning, depression, anxiety, dissociation, and aggression low drop-outs

Table II (Continued)

Authors/Journal	Subjects	Study design	Agent/Dose	Results
Zanarini et al. (2004c) J Clin Psychiatry	BPD $N=45$ females Excluded for major depression and bipolar disorder	RCT for 8 weeks Comparators: Olanzapine 2.5 mg Olanzapine + Fluoxetine	Fluoxetine (SSRI) 15 mg (average) Comparators: Olanzapine 3.3 mg (average) Olanzapine+Fluoxetine	Olanzapine alone and olanzapine in combination with fluoxetine turned out to be better on measurements of impulsive aggression and depression compared to fluoxetine alone low drop-outs

Low drop-outs, <15%; moderate drop-outs, 15% <x <50%; high drop-outs, ≥50%.

selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and irreversible monoamine oxidase inhibitors (MAOIs). To evaluate the efficacy of antidepressants, patients' responses have been assessed by applying observer-rating scales and self-rating scales on depression (HAM-D, POMS, BDI), anger and aggression (STAXI, OAS-R), anxiety (STAI), dissociation (DES), global functioning (GAF). Only a minority of studies included specific instruments to assess changes of BPD psychopathology, such as the BPD Severity Index (Rinne et al. 2002), the PD Disorder Rating Scale (Salzmann et al. 1995) and the Borderline Symptom Index (Soloff et al. 1989, 1993).

Nine RCTs testing the efficacy of antidepressants have been conducted so far (cf. Table II), one study including the tricyclic antidepressant amitryptiline (Soloff et al. 1989), one study mianserine (Montogomery and Montgomery 1982), two studies including irreversible MAOIs (Cowdry and Gardner (1988) and Soloff et al. (1993) for the acute and Cornelius et al. (1993) for the continuation phase) and five studies on SSRIs (four studies on fluoxetine (Salzmann et al. 1995; Coccaro and Kavoussi 1997; Simpson et al. 2004; Zanarini et al. 2004c) and one study on fluvoxamine (Rinne et al. 2002)). With the exception of mianserine, which was shown to have no better effect on outcome in 58 patients with suicidal acts (30 of them meeting the diagnosis of BPD) than placebo at any point in a 6-month double-blind trial when tested for its efficacy to reduce suicidal behaviour, significant improvements were consistently found over all studies for mood (depression) and anxiety, while evidence regarding the influence on impulsivity and aggression is not conclusive. SSRIs have shown a benefit for impulsive aggression in borderline patients with a comorbid condition of intermittent explosive disorder (IED) (Coccaro and Kavoussi 1997; New et al. 2004); however, data from BPD samples without IED are inconsistent (Rinne et al. 2002). Most, but not all, studies allowed the inclusion of patients with comorbid mood and anxiety disorders. From the two studies (Salzmann et al. 1995; Zanarini et al. 2004c) which excluded comorbid conditions with major depression and from the study performed by Rinne and colleagues (2002) one may conclude that antidepressants do not only influence the comorbid affective conditions, but also reduce depressive mood, anxiety and rapid mood swings. However, there are no data that tested for effects on emptiness, loneliness, boredom, chronic dysphoria and therefore experiences BPD sufferers often complain of. The clinician, therefore, needs to distinguish between true depressive symptomatology and

loneliness, emptiness, boredom, and chronic dysphoria. There is some evidence from clinical experience that one of the causes of polypharmacy may be when clinicians mistake the latter symptoms for treatment-resistant depression. Then the clinician attempts many different types and combinations of medications to try impact these symptoms although we do not know if they are responsive to any psychopharmacological agents. Finally, three studies reported an increase in global functioning.

In addition, the efficacy of olanzapine–fluoxetine combination was tested against monotherapy of fluoxetine and olanzapine. All three compounds turned out to be effective, reducing dysphoria and impulsive aggression in BPD patients. However, olanzapine monotherapy and the combination were found to be superior to fluoxetine monotherapy (Zanarini et al. 2004c). The only study that tested for an add-on effect of fluoxetine to an efficacious psychosocial treatment (Dialectical-Behaviour Therapy) provided no evidence for an additional effect of the added medication (Simpson et al. 2004). However, the medication placebo group showed significant improvement in clinician-rated global functioning and depression and clinically meaningful reductions in anxiety and dissociation, while no significant pre-posttreatment changes were found on any measure for the fluoxetine group. As this study was based on a small sample size of a total of 20 subjects making it very likely that the study was underpowered, further studies are needed to evaluate probable additional benefits of antidepressants to psychotherapy treatment. There is one further study on combined therapy in 32 patients with BPD, all of whom suffered from a comorbid condition of major depression. The combined treatment of interpersonal psychotherapy and fluoxetine turned out to be more effective, not only in the treatment of major depression but also in improving some dimensions of quality of life and interpersonal functioning (Bellino et al. 2006b).

Results from open trials should be interpreted with caution, since studies in BPD are particularly prone to high placebo response rates (Salzmann et al. 1995; Lieb et al. 2004). Regarding open-label trials and case series on antidepressants, four studies included SSRIs (two on fluoxetine (Norden et al. 1989, Markovitz et al. 1991) and one on venlafaxine (Markovitz et al. 1995). All studies, which were based on 12–45 patients, reported significant improvements of general psychopathology, and two of them further reported a reduction of self-injurious behaviour. In addition, a controlled, but not randomized trial was conducted in BPD, testing for the effect of the irreversible MAOI phenelzine in comparison to imipramine (Parsons et al. 1989).

Phenelzine was found to be superior to placebo and the tricyclic therapy.

On the whole, the database is rather limited, with sample sizes being small overall, meaning that only evidence level C is achieved for the tricyclic amitriptyline, for the irreversible MAOI phenelzine and for the SSRIs fluoxetine and fluvoxamine. However, amitriptyline and phenelzine were only tested in one placebo-controlled randomized trial, while six RCTs have been conducted with SSRIs. Therefore, evidence of efficacy is, relatively speaking, best for this newer generation of antidepressants including longer periods of observation (6–14 weeks), although sample sizes were restricted to less than 50 subjects throughout. In addition, the first meta-analysis of RCTs in BPD concludes a positive effect of antidepressants on affective instability (Nosè et al. 2006).

2.2.2 Comparative efficacy and tolerability. With the exception of one small placebo-controlled trial, which tested for the efficacy of phenelzine in comparison to imipramine and placebo (Parsons et al. 1989) in BPD (the majority of subjects not meeting with the criteria of a full-blown disorder), no comparative studies between antidepressants have yet been reported in BPD, meaning that no reliable conclusions can be drawn as to whether groups of antidepressants are equal in efficacy. In the case of non-response to a first SSRI, it is unknown whether another antidepressant will help, but patients may be switched to a second antidepressant with another pharmacological profile or an SNRI. Although the efficacy of irreversible MAOIs is supported by the RCT study that included the highest number of patients (Soloff et al. 1993), they are not considered first-line treatments because of the risk of a potentially fatal hypertensive crisis or serotonin syndrome when consuming tyramine-containing foods or due to toxicity in the case of suicidal overdose. Irreversible MAOIs are particularly prescribed with caution in a population characterized by rather low compliance and high impulsivity.

Side effects vary highly among classes of antidepressants. Selecting medication for borderline patients, clinicians should know that these patients suffer from obesity, hypertension and diabetes more frequently than the general population (Frankenburg and Zanarini 2004). The anticholinergic/antimuscarinergic side effects of TCAs should not be neglected either. Because of the difficulties known in keeping BPD patients on medication for sustained periods (cf. Lieb et al. 2004), BPD patients may discontinue treatment because of adverse effects. Particularly the toxic effects after overdose cause clinicians to consider

Table III. Randomized controlled trials on neuroleptics in borderline personality disorder.

Authors/ Journal	Subjects	Study design	Agent/Dose	Results
Goldberg et al. (1986) Arch Gen Psychiatry	$N=40$ BPD $N=17$ schizotypal PD $N=13$ comorbid condition $N=20$	RCT over 12 weeks	Thioridazine (CN) 5–40 mg 8.7 mg (average) vs. placebo	Data on the whole group: significant better on paranoia, psychotic behaviour as well as obsessions and compulsions, no effect on depression, anger, hostility moderate drop-outs
Cowdry & Gardner (1988) Arch Gen Psychiatry	BPD $N=16$ all with behavioural dyscontrol	RCT over 5 weeks	Trifluoperazine (CN) 7.8 mg (average) vs. placebo vs. tranylcypromine	Compared to placebo significantly improved behavioural control, reduction of anxiety and depression, no improvement of global functioning
Soloff et al. (1989) J Clin Psychopharma-col	BPD $N=90$ inpatients	RCT over 5 weeks Comparator: Amitriptyline	Haloperidol (CN) 4–16 mg Amitriptyline 100–175 mg	Significant improvement of global functioning, depression, hostility and schizotypal and impulsive symptoms compared to placebo low drop-outs
Soloff et al. (1993), Cornelius et al. (1993) Arch Gen Psychiatry, Am J Psychiatry	BPD $N=108$ Comorbid depression included	RCT including placebo over 5 weeks, followed by 16 weeks of continuation Comparator: Phenelzine (60 mg average)	Haloperidol (CN) 4 mg (average) vs. phenelzine	Haloperidol worse than phenelzine and placebo on depression, anxiety, anger, hostility, improvement only for irritability in acute and continuation phase 64% drop-outs from haloperidol in 16 weeks, moderate drop-outs the whole group
Zanarini & Frankenburg (2001) J Clin Psychiatry	BPD $N=28$ females no comorbidity with current depression, bipolar or schizophrenic disorder	RCT over 24 weeks	Olanzapine (AN) 5.3 ± 3.4 mg/d vs. placebo	Significant reduction of anxiety, anger, impulsivity, paranoia and interpersonal sensitivity, no effect on depression high drop-outs in both groups
Bogenschutz & Nurnberg (2004) J Clin Psychiatry	BPD $N=40$ females no comorbidity with depression, bipolar or psychotic disorder	RCT over 12 weeks	Olanzapine (AN) 6.9 mg/day (average) vs. placebo	Significant improvement of global BPD psychopathology (effect size = 0.77) with significant effect on anger, but not on psychotic-like symptoms (item level), no effect on depression, anxiety and aggressive behaviour high drop-outs in the olanzapine group, moderate drop-outs on placebo
Zanarini & Frankenburg (2004c) J Clin Psychiatry	BPD $N=45$ females no comorbidity with current depression, bipolar or schizophrenic disorder	RCT over 8 weeks	Olanzapine (AN) 3.3 mg (mean dose) Comparators: Fluoxetine 15 mg (mean dose) Olanzapine+Fluoxetine	Olanzapine alone and olanzapine in combination with fluoxetine turned out to be better on measurements of impulsive aggression and depression compared to fluoxetine alone low drop-outs

Table III (*Continued*)

Authors/Journal	Subjects	Study design	Agent/Dose	Results
Soler et al. (2005) Am J Psychiatry	BPD $N=60$ females no unstable Axis I disorder	RCT over 12 weeks	DBT+Olanzapine (AN) 8.83 mg/day (mean dose) vs. DBT+Placebo	Significant add-on effect on depression, anxiety, impulsive–aggressive behaviour; trend towards a significant effect on self-injurious behaviour moderate drop-outs in both groups
Nickel et al. (2006, 2007) Am J Psychiatry, Psychophar-rmacology	BPD $N=57$ acute phase $N=52$ continuation phase a number of comorbid conditions, no comorbidity with schizophrenia	RCT over 8 weeks acute phase and 18-month follow-up	Aripiprazole (AN) 15 mg/day vs. placebo	Significant effect on depression, anxiety, anger, aggressiveness, paranoia, and global functioning in acute and continuation phase no drop-outs in acute phase

CN, classical neuroleptic; AN, atypical neuroleptic; low drop-outs, <15%; moderate drop-outs, 15% <x <50%; high drop-outs ≥50%.

SSRIs as the first-line agent in a population prone to parasuicidal gestures and suicide attempts.

2.3 Treatment with neuroleptics (cf. Table III)

2.3.1 Classification and efficacy. Neuroleptics could be effective for distortions in the cognitive–perceptual realm. In addition, evidence has been provided that atypical neuroleptics and second-generation antipsychotics can also exert a stabilizing effect on mood and anxiety, probably due to their high 5HT1a receptor affinity and that, possibly, due to their antagonistic effect at 5-HT2a receptors (e.g., aripripazole, clozapine, olanzapine, risperidole, ziprasidone), they can also diminish impulsivity and aggression. In BPD, RCTs for both classical neuroleptics such as haloperidol and flupenthixol as well as atypical neuroleptics such as olanzapine, and aripripazole have been published. For the evaluation of the efficacy of neuroleptics, measurements have frequently been applied that assess broad aspects of psychopathology (SCL-90), including paranoid ideation, psychotic thought, anger/hostility, and interpersonal sensitivity. Scales on global social functioning have also been frequently utilized (GAF). In addition, scales on specific features of psychopathology have been included, mostly for the assessment of anger and aggression (STAXI, AIAQ, OAS), for depression (BDI, HAM-D, MADRS), and sometimes for dissociation (DES). The assessment of changes in self-injurious and other forms of self-harming behaviour and therefore of the clinically most severe symptoms of BPD has only been included in the study by Soler et al. (2005).

Nine RCTs have been conducted to test for the efficacy of neuroleptics in BPD (cf. Table III), four placebo-controlled studies on classical neuroleptics (Goldberg et al. 1986; Cowdry and Gardner 1988; Soloff et al. 1989; Cornelius et al. 1993; Soloff et al. 1993) including thioridazine (one study), haloperidol (two studies) and trifluoperazine (one study) and five placebo-controlled studies on atypical neuroleptics (four on olanzapine (Zanarini and Frankenburg 2001, 2004c; Bogenschutz and Nurnberg 2004; Soler et al. 2005) and one on aripripazole (Nickel et al. 2006, 2007)). Regarding haloperidol, only Soloff and colleague's first study was followed by improvement of psychotic-like symptoms, while the latter one, although similar in sample seize, demonstrated efficacy only for the treatment of irritability. Thioridazine was reported to have a positive effect on paranoia, while outcome measures in the trifluoperazine study did not include measures of paranoia and other psychotic-like symptoms. Therefore, classical neuroleptics have not been consistently followed by improvement of

psychotic-like symptoms and a reduction of affective symptoms was only reported from the one study on trifluoperazine by Cowdry and Gardner (1988). In addition, short-term effects of haloperidol were not maintained in an 11-week open-label follow-up (Soloff
et al. 1993). Regarding the atypical neuroleptics, a consistent effect was shown on cognitive-perceptual symptoms, anger and impulsivity. Two studies failed to show a significant reduction of depression and anxiety, while one was unable to find an effect on aggressive behaviour. Studies not only on classical neuroleptics but also on atypical neuroleptics were weakened due to moderate to high drop-out rates.

Discontinuation of medication was particularly high in long-term treatments (> 8 weeks), rendering it impossible to determine whether the effects of atypical antipsychotics persist, diminish, or increase with time. First- and second-generation neuroleptics appear to work at lower doses than in schizophrenia (ct. Table III) although no studies have focused on finding the optimal dosage for patients with BPD.

In addition to RCTs, 10 open-label studies on atypical neuroleptics have been performed in BPD, three on clozapine (Frankenburg and Zanarini 1993; Benedetti et al. 1998; Chengappa et al. 1999), four on quetiapine (Gruettert and Friege 2005; Villeneuve and Lemelin 2005; Bellino et al. 2006a; Perrella et al. 2007), one on olanzapine (Schulz et al. 1999), one on risperidone (Rocca et al. 2002), and one on ziprasidone (Pascual et al. 2004). Most of these studies included only very small sample sizes of between nine and 15 patients, and the study by Perrella et al. included 29 outpatients. One open-label trial on flupenthixole was performed in 45 patients. All studies reported improvement of psychopathology, mostly of depression, impulsivity, anger, aggression, and psychotic symptoms.

Although neuroleptics data are based on larger sample sizes compared to the data on antidepressants, the database is still rather small. The efficacy of atypical neuroleptics is indicated on a fair research-based evidence level (Level B). In addition, first evidence for an add-on effect was provided in the study by Soler et al. (2005), who found an additional effect of olanzapine on depression, anxiety and impulsive-aggressive behaviour in a sample of female patients who were treated with dialectic-behavioural therapy. The database provides no reliable comment on the magnitude of effect.

2.3.2 Comparative efficacy and tolerability. Among atypical neuroleptics, olanzapine is by far the best investigated agent. However, no differential effect can be concluded, since no comparative studies between atypical neuroleptics have been conducted in BPD to date. However, there is an early study, comparing the classical neuroleptics haloperidol versus thiothixen (Serban and Siegel 1984). Further comparative studies tested an antipsychotic, i.e. haloperidol, with the irreversible MAOI phenelzine (Soloff et al. 1993) and the TCI amitriptylin (Soloff et al. 1989), and indicated better results for amitryptilin on depression only while phenelzine turned out to better act on borderline psychopathology as well. In a double-blind, crossover trial of alprazolam, carbamazepine, trifluoperazine and placebo (Cowdry and Gardner 1988) patients rated themselves as improved relative to placebo only while receiving tranylcypromine, while physicians rated improvement in response to tranylcypromine and carbamazepine; those receiving alprazolam had an increase in the severity of the episodes of serious dyscontrol. In addition, the atypical agent olanzapine was tested against fluoxetine with olanzapine monotherapy and the combination being superior to fluoxetine monotherapy.

In addition to questionable evidence of efficacy, the application of classical neuroleptics is also restricted because of frequently occurring extrapyramidal side effects, which stigmatize patients and may lead to serious handicaps in the form of tardive dyskinesia. Therefore, atypical neuroleptics can be regarded as the first-line treatment of cognitive-perceptual symptoms in BPD. Furthermore, data indicate a positive effect of atypical neuroleptics on anger and impulsivity consistently over all studies and there is one study which showed a superior effect of olanzapine monotherapy (and a combination of olanzapine and fluoxetine) compared to fluoxetine alone on impulsive aggression (Zanarini et al. 2004c). Further studies are needed to test whether atypical neuroleptics rather than SSRIs may be established as the first-line treatment to reduce anger and impulsivity. Contrary to the highly consistent results on cognitive disturbance and impulsivity, data on the influence of the affective disturbance in BPD patients are mixed.

Although atypical neuroleptics have milder side effect profiles than classical neuroleptics, they do have considerable side effects. From all studies on olanzapine, significant weight gain between 2.7 and 3.7 kg within 12 weeks was reported. As 29–53% of borderline patients fulfil the lifetime criteria of an eating disorder (mostly bulimia nervosa) (Lieb et al. 2004) and as a major number suffer from obesity (Frankenburg and Zanarini 2006), the provocation of obesity must be regarded as a serious disadvantage. In addition, disadvantageous influences on weight, glucose and cholesterol have well-known long-term effects on an individual's cardiovascular

Table IV. Randomized controlled trials on mood stabilizer in borderline personality disorder.

Authors/Journal	Subjects	Study design	Agent/Dose	Resultants
Cowdry & Gardner (1988) Arch Gen Psychiatry	BPD $N=16$♀ No current major depression	Randomized crossover-trial; each trial for 6 weeks	1. phase: placebo vs. alprazolam vs. carbamazepine 2. phase: trifluoperazine vs. tranylcypromine	Significant overall improvement reported by physicians on tranylcypromine and carbama-zepine, reported by patients only on tranylcypromine; decrease of behavioural dyscontrol on carbamazepine, increase on alprazolam
De la Fuente & Lotstra (1994) Eur Neuropsychopharmacol	BPD $N=20$ no comorbidity	RCT over 4.5 weeks	Carbamazepine 6.44–7.07 µg/ml (average plasma level) vs. placebo	No effect
Hollander et al. (2001) J Clin Psychiatry	BPD $N=21$ excluded for psychotic and bipolar disorders and for current major depression	RCT over 10 weeks	Divalproex sodium 80 µg/ml (plasma level) vs. placebo	No significant group effect; but reduction in aggression and depression only in subjects treated with divalproex sodium small number of completers high drop-outs in both groups
Frankenburg & Zanarini (2002) J Clin Psychiatry	BPD $N=30$ females with comorbid bipolar II disorder, excluded for major depressive or hypomanic episode	RCT 28 weeks	Divalproex sodium 50–100 µg/ml (plasma level) vs. placebo	Significant improvement in anger/hostility, interpersonal sensitivity and aggression, no effect on depression small number of completers; high drop-outs in both groups
Hollander et al. (2003, 2005) Neuro-psychopharmacology, Am J Psychiatry	Cluster B PD with impulsive aggression $N=96$ ($N=52$ BPD) excluded for bipolar I and II disorders and current major depression	RCT over 12 weeks	Divalproex sodium 80–120 µg/ml (plasma level) vs. placebo	Significant reduction of aggres-sion, irritability and depression, the effect higher among those with high trait impulsivity moderate drop-outs in the verum, low drop-outs in the placebo group
Tritt (2005) J Psychopharmacology	BPD $N=27$ females excluded for bipolar disorder and major depression	RCT over 8 weeks	Lamotrigin titrated to 200 mg/day vs. placebo	Significant reduction of all anger (STAXI) scales (except anger-in) low drop-outs
Nickel et al. (2004) J Clin Psychiatry	BPD $N=31$ females excluded for bipolar disorder and major depression	RCT over 8 weeks	Topiramat titrated to 250 mg/day vs. placebo	Significant reduction of all anger (STAXI)scales (except anger-in) low drop-outs
Nickel et al. (2005) Biol Psychiatry	BPD $N=42$ males excluded for bipolar disorder and major depression	RCT over 8 weeks titrated to 250 mg/d	Topiramat titrated to 250 mg/d vs. placebo	Significant reduction of all anger (STAXI)scales (except anger-in) no drop-outs
Loew et al. (2006) J Clin Psychopharmacol	BPD $N=56$ females no exclusion for mood disorders	RCT over 10 weeks	Topiramat titrated to 200 mg/d vs. placebo	Significant decrease on the somatization, interpersonal sensitivity, anxiety, hostility, phobic anxiety and global functioning SCL–90 subscales low drop-outs

Low drop-outs, $<15\%$; moderate drop-outs, $15\% <x <50\%$; high drop-outs, $\geq 50\%$.

condition. A significant weight gain, however, does not appear to be a general side effect of atypical neuroleptics in this population, since BPD patients under aripripazole were found to remain stable in weight (Nickel et al. 2006).

2.4 Treatment with mood stabilizers (cf. Table IV)

2.4.1 Classification and efficacy. Within the last years, a number of mood stabilizers have been tested in RCTs for efficacy in BPD: carbamazepine (De la Fuente and Lotstra 1994), divalproex sodium (Hollander et al. 2001, 2003, 2005; Frankenburg and Zanarini 2002) topiramate (Nickel et al. 2004, 2005; Loew et al. 2006), and lamotrigine (Tritt 2005). The only small study to test the effect of carbamazepine found no evidence for a significant effect on psychopathology; however, this study consisting of 20 patients might be underpowered. While the results were inconsistent for divalproex sodium in pure BPD conditions, there might be an effect in the case of comorbidity with bipolar II disorder, as one study including a rather small sample suggests (Frankenburg and Zanarini 2002) (Level C). In addition, one RCT in a sufficiently large sample suggests that divalproex sodium is suitable in borderline and other cluster B subjects with high trait impulsivity to reduce aggression, impulsivity and depression (Hollander 2003, 2005) (Level C). In addition, lamotrigine and topiramate were found to exert a positive effect on anger and reactive aggression in BPD, as measured by means of the STAXI (Nickel et al. 2004, 2005). The effect of topiramate was confirmed not only for female but also for male BPD patients and it was based on three RCTs (from the same group), although only one included more than 50 patients (Level C). No other psychopathological symptoms typical of BPD were investigated in these studies. Concerning lithium, one controlled study in BPD was carried out in 1990, which failed to demonstrate efficacy; although this empirical base is not sufficient to evaluate the suitability of lithium for this patient group, toxicity is too high to desire a broad application in BPD (Links et al. 1990).

In addition to RCTs three open-label studies have been conducted on the efficacy of divalproex in BPD patients. While Stein et al. (1995), using divalproex sodium, as well as Simeon et al. (2007), using divalproex extended-release, reported significant improvement of irritability, aggression and general psychopathology but not of other measurements of specific BPD symptoms from their studies of 11 and 13 outpatients, respectively, Wilcox et al. (1995) reported the greatest effect on anxiety and agitation in addition to a decrease of general psychopathology

in 30 subjects with BPD. One open-label study in 17 BPD outpatients was performed on oxcarbazepine with improvement observed for affective instability, impulsivity and anger outbursts.

2.4.2 Comparative efficacy and tolerability. No comparator study has been published to date with the exception of the randomised crossover study by Cowdry and Gardner (Section 2.3.2) including carbamazepine. On the whole, data from studies on the efficacy of mood stabilizers in BPD suggest that these substances are helpful in modulating behavioural dyscontrol in highly impulsive individuals and should be tested more intensively against irritability and impulsive aggression in males and females with cluster B personality disorders. Whether topiramate has advantages compared to divalproex sodium and lamotrigine has to be clarified in suitable study designs. Present evidence suggests that mood stabilizers may be more effective for impulsive, aggressive behaviour than for mood stabilization (Paris 2005). However, as most of the studies were limited to the inclusion of measurements of anger and reactive aggression, no firm inferences can be drawn regarding influences on affective instability. In addition, mood stabilizers were indicated in the case of comorbidity with bipolar I and bipolar II disorders, which may exist in 10–25% of patients with BPD (Gunderson et al. 2006), although further studies are necessary to clarify the association between these disorders.

The necessity to titrate the dosage of mood stabilizers until the optimal plasma level has been reached, a procedure that needs up to 6 weeks for the new mood stabilizer generation, challenges high compliance in patients and might limit broad application in BPD. In addition, side effects of mood stabilizers need to be considered and can be dangerous on overdose. Typical side effects differ among the substances. Divalproex sodium may lead to weight gain, tremor, hair loss, suppression of blood cell proliferation, hepatic dysfunction and allergic reactions. For topiramate, the most commonly reported side effects were: dizziness, fatigue, somnolence, cognitive impairment in addition to reduced appetite, weight loss and paraesthesia (Nickel et al. 2004, 2005). The potential worsening of cognitive performance could limit the long-term use of this mood stabilizer, although none of the participants dropped out due to side effects. However, patients might have tolerated the side effects including cognitive decline in order to get the weight loss. In the study by Tritt et al. (2005), mild side effects were reported from lamotrigine: mild rash, dizziness, headache and nausea, although more serious adverse events are known from larger clinical

studies including severe allergic responses, movement disorders and visual handicaps.

2.5 Other pharmacological approaches

2.5.1 Classification and efficacy. Other pharmacological agents have been used in BPD. Zanarini and Frankenburg (2003) studied the efficacy of 1 g/day omega-3 fatty acids in an 8-week RCT including 30 female volunteers with BPD. Compared to control subjects, BPD patients taking omega-3 fatty acids experienced a greater reduction of depression and aggression, as measured with the Modified Overt Aggression Scale. The positive effect on aggression reported from BPD patients is consistent with an anti-aggressive effect that could be observed in two double-blind, placebo-controlled trials in healthy subjects (Hamazaki et al. 1996, 2002). Since a single study does not provide sufficient evidence to recommend omega-3 fatty acids as an antiaggressive medication (Level D), further controlled studies should be performed in the future. Omega-3 fatty acids may act by inhibiting protein kinase C, a mechanism that has also been attributed to mood stabilizers such as lithium and valproate acid (Peet and Stokes 2005). In the case of comorbidity with attention deficit/hyperactivity disorder, which may potentiate the behavioural implications of impulsivity in BPD, methylphenidate or atomoxetine might be indicated. Further studies have to clarify whether psychostimulants may deteriorate affective symptoms in BPD as suggested by an older case report indicating dysphoric episodes after acute administration of intravenous methylphenidate in a double-blind manner in two patients with BPD (Lucas et al. 1987).

Further agents have been tested for their efficacy against distinct borderline-typical symptoms. Clonidine was found to reduce aversive tension in 14 female BPD patients in an open (randomized, single-blind study (Philipsen et al. 2004) (Level D). The opiate antagonist naltrexone has been reported to reduce dissociative experiences in BPD (Bohus et al. 1999, although this observation has not yet been replicated in randomized placebo-controlled studies (Level D). One double-blind study did not show efficacy of i.v. application of naloxone in the treatment of acute states of aversive tension and dissociation (Philipsen et al. 2004).

Benzodiazepines are strongly discouraged in patients with BPD, as they can lead to sedation, cognitive and motor impairment, and may interact negatively with psychotherapy. In addition, paradoxical, disinhibitory effects have been reported from BPD patients (Cowdry and Gardner 1988; Moeller 1992) and may rather enhance than diminish the risk of severe suicide attempts. In addition, the risk of psychological and physical dependency may be higher than in episodic axis I disorders who may abuse benzodiazepines in frequently occurring states of highly aversive tension.

2.6 Psychotherapy

Studies on effectiveness of psychotherapeutic interventions meet some special methodological restrictions inherent to psychotherapy research because trials are never performed in a double-blind and placebo-controlled manner. Therefore, when comparing psychotherapeutic to pharmacological trials, these differences in approach should be taken in consideration. In case one strictly applies the the WFSBP guideline classification of evidence, level A – which demands at least one randomised, placebo-controlled group study – has no chance to be achieved. Therefore, in order to be able to work out the differences in the level of evidence between different psychotherapeutic treatments, we decided to classify those psychotherapies which among other preconditions were tested in a randomized controlled trial against treatment-as-usual (as the golden standard in psychotherapy research) as fulfilling the level A criterion.

In spite of the methodological restrictions described above and the small number of randomized controlled trials that have assessed the efficacy of psychotherapeutic interventions, the empirical database is broader regarding psychosocial than pharmacological treatments in BPD. Dialectic-behavioural therapy (DBT) was tested for efficacy compared to treatment-as-usual in six RCTs and compared to other psychotherapies in two further well-controlled trials, most of them covering an observation period of 1 year (Linehan 1991/1994, 1999, 2002, 2006; Turner 2000; Koons et al. 2001; Verheul et al. 2003; van den Bosch et al. 2005). In addition, six non-randomized controlled studies were also performed comparing DBT (including inpatient treatment) with treatment-as-usual. Improvement was consistent over all studies and was particularly indicated by a decrease in self-harming and parasuicidal behaviour, less time in hospital, lower depression and hopelessness and higher overall social functioning. There is good research-based evidence for the efficacy of DBT (Level A) in reducing self-harming and suicidal behaviour in BPD within the first year of treatment, and van den Bosch et al. (2005) reported sustained efficacy on parasuicidal and impulsive behaviours and on alcohol use at 6 months follow-up after discontinuation of DBT. Further studies have to be performed to provide more information on the long-term outcome of DBT and

other aspects of psychopathology, particularly on affective instability and interpersonal disturbance. In addition, only the first stage of the DBT program, in which parasuicidal behaviours and affect regulation are targeted, has been tested to date. Turner (2000) compared DBT with client-centred psychotherapy and found DBT to be superior with regard to impulsive and parasuicidal behaviours as well as depression. In addition, several programmes, some of them being a synthesis of DBT and family therapy, have been developed for families with a BPD member; preliminary data point to a positive effect; however, RCTs have not been performed, up to now.

Recently, the effectiveness of schema-focused therapy (SFT) developed by Young has been tested in a randomized controlled study against a psychodynamically based psychotherapy, i.e. transference-focused therapy (TFT), including a fairly large sample of $N = 88$ BPD patients (Giesen-Bloo et al. 2006). At the end of the treatment period of 3 years, clinical outcome measures showed significant improvement for both groups, although significantly more patients recovered under schema-focused therapy or exhibited reliable clinical improvement compared to the TFP group. Some evidence for the efficacy of SFT had already been reported previously from a case series (Nordahl and Nysaeter 2005), meaning that on the whole, the present data point to evidence level C and have to be replicated in further RCTs. Regarding the empirical database on TFP, the data from an RCT comparing this kind of structured psychodynamic therapy to DBT and supportive therapy points to the effectiveness of all three therapy interventions in multiple and clinically relevant domains of functioning across a 1-year period (Clarkin et al. 2007). Significant improvements under TFT were also reported from a preceding uncontrolled study over 1 year (Clarkin et al. 2001) (evidence level C).

There are further cognitive treatments for borderline personality disorder which have shown effectiveness in RCTs compared to treatment-as-usual. Manual assisted cognitive therapy (MACHT) is a short-term individual therapy which was developed to treat parasuicidal patients and which has been modified to focus on deliberate self-harm in BPD patients (Weinberg et al. 2006). Results of a small study with $N = 15$ BPD patients per study arm indicated that this therapeutic intervention was associated with significantly less frequent and less severe deliberate self-harm at completion of therapy and at 6 months follow-up; further studies in larger samples are needed (evidence level D). Cognitive behaviour therapy in addition to treatment as usual was compared to treatment as usual in 106 BPD subjects (Davidson et al. 2006). Over 12 months treatment, 27 therapy sessions were offered and 16 sessions were attended on average. Across both treatment arms improvement was found with benefit for the addition of cognitive behaviour therapy on distress at 1 year, and on anxiety, dysfunctional beliefs and the frequency of suicidal acts at 2-year follow-up. Together with the results of an uncontrolled clinical trial, which revealed significant decreases on affective and borderline symptoms as well dysfunctional beliefs in a BPD sample of 32 patients at termination and 6-month follow-up (Brown et al. 2004), there is minimal research-based evidence (level C) for effectiveness of cognitive behaviour therapy in BPD.

An RCT of a further psychodynamic therapy was conducted compared to treatment-as-usual in general psychiatric services by Bateman and Fonagy (1999, 2001). 'Mentalization-based therapy' was tested in a day-hospital setting at the end of treatment at 18 months and with a follow-up after a further 18 months and at both assessment times was shown to be effective in reducing inpatient days, depression, anxiety and global severity of psychopathological symptoms. In addition, significantly more BPD patients had refrained from self-mutilation and suicidal acts. Effectiveness was not shown for borderline-specific variables. The database is restricted to one RCT (level D).

Since longitudinal studies suggest that BPD tends to improve with time, future studies have to clarify whether long-term psychotherapeutic and pharmacological treatments make this process occur more rapidly (Paris 2005). A meta-analysis of treatment studies in personality-disordered patients, which compared results with rates of naturalistic recovery, concluded in 1999 that psychotherapy provides a clear advantage to the naturalistic course (Perry et al. 1999). Similar studies have to be conducted using more data from controlled studies.

2.6.1 Combining pharmacotherapy with psychotherapy. Similar to other psychiatric disorders, clinical practice for BPD patients often includes a combination of pharmacotherapy and psychotherapy. Most RCTs on the efficacy of pharmacological agents included patients who also received psychotherapy. However, in BPD, there are only two studies that have tested for the additive effects of pharmacological agents to the benefit of psychotherapy. While an add-on effect could be found for olanzapine, which was combined with dialectic-behavioural therapy (Soler et al. 2005), this additive effect was not confirmed for the antidepressant fluoxetine (Simpson et al. 2004); however, this study was apparently underpowered. A study by Bellino et al. (2006b) (ct. Section 2.2.1)

compared fluoxetine monotherapy to a combined therapy of fluoxetine and interpersonal therapy in 32 patients with BPD all of whom suffered from a comorbid condition of major depression. Combined therapy was only more effective in reducing depression and improving some dimensions of quality of life and interpersonal functioning. On the whole, there is not much of an evidence-base on when/how to combine pharmacotherapy/psychotherapy. More research with sufficiently powered study designs is necessary to clarify the benefits of combination therapies and to elucidate similarities and differences in the biological mechanisms underlying the two treatment approaches, psychopharmacotherapy and psychotherapy.

When including medication in the psychotherapeutic treatment of BPD patients, one should explain its targets precisely and should consider probable effects it could have on the therapeutic alliance and the patient's idea of self-efficacy. In addition, since borderline patients are prone to seeing issues in 'either-or' categories, combined treatment introduces the possibility that the patient will seize upon, and alternate between, a purely 'biological' and a purely 'psychological' view of the disorder, using each perspective to undercut the other. Therefore, active work by the therapists to integrate the two modalities forestalls such a complication (Koenigsberg 1991). Medication can well be integrated in a problem-solving orientation so

Table V. Classification and criteria of schizotypal personality disorder according to DSM-IV.

Schizotypal Personality Disorder

A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behaviour, beginning in early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Ideas of reference (excluding delusions of reference).
2. Odd beliefs or magical thinking that influences behaviour and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or 'sixth sense'; in children and adolescents, bizarre fantasies or preoccupations).
3. Unusual perceptual experiences, including bodily illusions.
4. Odd thinking and speech (e.g., vague, circumstantial, metaphorical, overrelaborate, or stereotyped).
5. Suspiciousness or paranoid ideation.
6. Inappropriate or constricted affect.
7. Behaviour or appearance that is odd, eccentric, or peculiar.
8. Lack of close friends or confidants other than first-degree relatives
9. Excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self.

Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder.

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that the patient's responsibility to actively engage in a process of change and development is not hindered.

2.7 Treatment of adolescents with borderline personality disorder

As first symptoms of BPD usually start in early or middle adolescence, and as early detection and treatment intervention is important in improving the outcome of BPD, the specific conditions of adolescents exhibiting a full-blown or a subthreshold symptomatology of BPD need to be considered. Despite the theoretical potential for benefit from an early therapeutic intervention to BPD, no pharmacological studies have been performed in adolescents to date. From RCTs of depression in children and adolescents, the efficacy of tricyclic medication appears to be less convincing than in adults (Hazell et al. 2001) and the effect appears to be weaker than in response to SSRIs (Bauer et al. 2002). However, increased aggression and particularly an intermittent increase of suicidal behaviour challenge close monitoring, especially early in treatment (Wong et al. 2004).

Due to the absence of empirical data in adolescents, recommendations from adults' pharmacological approaches may also be used for BPD adolescents with careful consideration of a probably greater risk of adverse effects. In the case of non-response to SSRIs and dominating impulsive-aggressive behaviour, atypical neuroleptics may be indicated, with risperidone being the agent that is relatively best tested in adolescence (however, only in psychotic disorders).

3 Schizotypal personality disorder

3.1 Diagnosis, epidemiology and course of schizotypal personality disorder (cf. Table V)

Schizotypal personality disorder (STPD) is characterized by pervasive social and interpersonal deficits and by subtle, psychotic-like symptoms. Patients' social impairment results from a difficulty in reading social cues, from intense social anxiety, and an odd, eccentric appearance. With regard to psychotic-like features, one may differentiate between positive-like, i.e. vulnerability to suspiciousness, ideas of reference, paranoid ideation, unusual experiences and odd beliefs, and negative-like symptoms, i.e. vague, over-elaborate or stereotyped speech with a sometimes metaphorical choice of words, inappropriate or constricted affect, and anhedonia). Longitudinal data over 2 years suggest that the positive-like symptoms are the more stable, trait-like features, while constricted affect and inappropriate, odd

behaviour are most changeable (McGlashan et al. 2005). Patients with schizotypal personality disorder usually exhibit a low level of occupational functioning and at best work at occupations considerably below their levels of education. This category is only found in DSM-IV. The rather similar concept of schizotypal disorder is conceptualized as a schizophrenia-related disorder in ICD-10 and there is actually high consistency in genetic and neurobiological data that schizotypal personality disorder can be reasonably regarded as a schizophrenia-spectrum disorder.

Prevalence is estimated to occur in up to 3% of the general population and implies an appreciable social cost and public health impact (Koenigsberg et al. 2003). With regard to psychiatric comorbidities, patients tend to suffer from anxiety and depressive disorders and some of them also fulfil the criteria of borderline, paranoid and avoidant personality disorder.

There are a number of biological data that suggest that STPD is a schizophrenic spectrum disorder: higher risk for schizophrenia-related disorders in first-degree relatives, deficits in prepulse inhibition and P50 suppression, and antisaccade paradigms. In addition, patients have been reported to show a number of cognitive deficits in working memory, in particular sustained attention and executive functioning (Parc and McTigue 1997; Bergida and Lenzenweger 2006; McClure et al. 2007). However, there are also differences; while schizotypal patients, like schizophrenic patients, show reductions in temporal lobe volume and reduced striatal dopaminergic activity, neuroimaging data propose that that there may be preservation of frontal lobe volume in subjects with schizotypal personality disorder (Siever and Davis 2004). Longitudinal data over 2 years suggest a rather low stability in diagnosis, with only 34% remaining above the threshold of the disorder. However, schizotypal subjects have the lowest level of functioning compared to borderline, avoidant and obsessive-compulsive personality disorder in the short and long term, and their functional impairment improves less than psychopathology but remains poor with regard to employment functioning in particular (Skodol et al. 2005).

3.2 Treatment with neuroleptics

3.2.1 Classification and efficacy. Similarities between STPD and schizophrenia-related disorders in phenomenology and biology have provided the rationale for testing the efficacy of neuroleptics in STPD. One RCT of thioridazine included $N = 13$ patients with STPD without BPD, although response data with a significant improvement in psychotic symptoms were only reported for the whole group of BPD, STPD and comorbid patients (Goldberg et al. 1986). One well-controlled study including 25 patients with STPD (only five of whom had comorbid BPD) suggested a potency of risperidone in reducing 'positive' and 'negative' symptoms, but not depression in STPD (Koenigsberg et al. 2003).

Three open-label studies have been published of low doses of classical neuroleptics, such as haloperidol and thiothixene in STPD, with most patients fulfilling the criteria not only for STPD but also for BPD. Recently, a 26-week, open-label study with flexible dose of olanzapine in 11 patients with SPD reported a significant improvement in psychosis and depression ratings as well as in overall functioning; no data on comorbid axis II disorders were given in this study (Keshavan et al. 2004).

On the whole, there is some evidence that atypical neuroleptics may be effective in reducing symptom severity in STPD (Level C). In addition, there is some evidence from open-label studies that point to an effect of low-dose classical neuroleptics (evidence level D).

3.3 Treatment with antidepressants

There has been an open-label trial of fluoxetine in a small sample of patients diagnosed with STPD, BPD, or both, which showed improvement in depression, anxiety, interpersonal anxiety, interpersonal sensitivity, and psychoticism, but only four of the 22 patients had STPD without a comorbid condition of BPD (Markowitz et al. 1991). Therefore, there is no reliable evidence for the efficacy of antidepressants in the treatment of schizotypal symptoms.

4 Anxious/avoidant personality disorder

4.1 Diagnosis, epidemiology and course of anxious/avoidant personality disorder (cf. Table VI)

Anxious/avoidant personality disorder (AVPD) is characterized by social phobia, poor self-esteem, rejection sensitivity and pronounced avoidance behaviour. Subjects appear inhibited in a great variety of social situations, they are highly sensitive towards criticism and negative evaluation and suffer from feelings of inferiority and being inadequate. They need to be certain of being liked before making social contacts and worry about shame and risks of exposure.

AVPD together with BPD is the most common personality disorder with prevalence rates of up to 1.5% in the general population and between 10 and 15.2% among psychiatric patients (Loranger 1994). Patients exhibit high comorbidity with depressive

Table VI. Classification and criteria according to DSM-IV (Avoidant Personality Disorder) and ICD-10 (Anxious [Avoidant] Personality Disorder).

ICD-10 (research criteria)	DSM IV

F60.6 Anxious [avoidant] personality disorder
A. The general criteria of personality disorder (F60) must be met.
B. At least four of the following must be present:
  1. Persistent and pervasive feelings of tension and apprehension.
  2. Belief that oneself is socially inept, personally unappealing, or inferior to others.
  3. Excessive preoccupation about being criticized or rejected in social situations.
  4. Unwillingness to get involved with people unless certain of being liked.
  5. Restrictions in lifestyle because of need of security.
  6. Avoidance of social or occupational activities that involve significant interpersonal contact, because of fear of criticism, disapproval or rejection.
	Avoidant Personality Disorder
	A pervasive pattern of social inhibition, feelings of inadequacy and hypersensitivity to negative evaluation, beginning in early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:
	  1. Avoids occupational activities that involve significant interpersonal contact, because of fears of criticism, disapproval, or rejection.
	  2. Is unwilling to get involved with people unless certain of being liked.
	  3. Shows restraint within intimate relationships because of the fear of being shamed or ridiculed.
	  4. Is preoccupied with being criticized or rejected in social situations.
	  5. Is inhibited in new interpersonal situations because of feelings of inadequacy.
	  6. Views self as socially inept, personally unappealing, or inferior to others.
	  7. Is unusually reluctant to take personal risks or to engage in any new activities because they may prove embarrassing.

disorders (Parker et al. 1998) and AVPD is a comorbid condition in up to one-third of all patients with anxiety disorders (Alden et al. 2002), particularly generalized anxiety and panic disorders. Feeling inadequate and socially inept appears to be the most stable and trait-like feature of this personality disorder, with first symptoms often starting in childhood as shyness and behavioural inhibition. Recent data suggest that AVPD is a particularly stable personality disorder, with 56% of patients remaining at or above threshold after two years and showing little improvement over time, at least as suggested by empirical data from a two-year observation period (Skodol et al. 2005).

There is a great conceptual and empirical overlap of AVPD with the generalized subtype of social phobia, the latter referring to social anxiety and avoidance behaviour that extend to most social situations. A number of findings from empirical studies support the conceptualization of AVPD and social phobia as quantitatively different disorders falling along the same spectrum of disease (Dolan-Sewell et al. 2001). A number of authors argue that subjects with AVPD are more severely handicapped with higher social anxiety and greater levels of depression than those with social phobia (Herbert et al. 1992), while others suggest that social phobia is a complication or an associated feature of AVPD (Widiger et al. 1992). However, there are also authors who recommend that AVPD should be removed from axis II on the grounds of

an almost total overlap with the axis I diagnosis (Ralevski et al. 2005).

Up to now, no neurobiological research has been performed in AVPD and there is no evidence that models of aetiology which have been developed for social anxiety disorder (including dysfunctioning of the amygdala, prefrontal cortex, hippocampus and striatum) can be transferred to AVPD. In addition, there is no knowledge whether allelic polymorphisms concerning the serotonin transporter and catechol-*O*-methyl transferase thought to play a prominent role in social phobia also have aetiologcal relevance for AVPD.

High overlap between the disorders suggest that it is justified to extrapolate from data which are primarily related to anxiety disorders and not personality disorders data and to apply treatment strategies for AVDP that have primarily been developed for social phobia. To date, no RCT on patients fulfilling the full criteria of AVPD has been published. The majority of studies testing for the efficacy of antidepressants in social phobia have included data on the percentage of cases meeting the criteria of the generalized subtype and at least four studies included measurements of personality pathology. These studies show that there is no difference in response between the social phobics with and without comorbid AVPD, with a tendency for the comorbid group to show even a greater drug/placebo difference. In Table V the percentage of comorbidity with AVPD is indicated in case it has been taken into consideration.

Table VII. Randomized controlled trials on antidepressants in social phobia (none of them being performed in groups defined by anxious/avoidant personality disorder).

Authors/Journal	Subjects	Study design	Agent/Dose	Results
Versiani et al. (1992) Br J Psychiatry	N=78 Social phobia[1]	RCT over 16 weeks	Phenelzine (irrev. MAOI) 67.5 mg/day vs. Moclobemide 580 mg/day vs. placebo	Both agents better than placebo on social phobia and social functioning Responders 82% in the moclobemide and 991% in the phenelzine group moderate drop-outs in both groups
van Vliet et al. (1994) Psychopharmacol	N=30 Social phobia 53% generalized form	RCT over 12 weeks	Fluvoxamine (SSRI) 150 mg vs. placebo	Reduction of social and general anxiety, not of phobic avoidance no drop-outs
Katzelnick et al. (1995) Am J Psychiatry	N=12 Social phobia[1]	RCT over 10 weeks cross-over design	Sertraline (SSRI) 50–200 mg vs. placebo	Reduction of social anxiety, bodily pain, increase in social functioning no drop-outs
Fahlen et al. (1995) Acta Psychiatr Scand	N=77 Social phobia[1]	RCT over 12 weeks	Brofaromine (RIMA) 150 mg vs. placebo	Reduction of anxiety, avoidance, depression low drop-outs
IMCTGMSP Katschnig (1995) Eur Arch Psychiatry Clin Neurosci	N=578 Social phobia 78% generalized form 49% AVPD	RCT over 12 weeks	Moclobemide (RIMA) 300 or 600 mg vs. placebo	Reduction of social anxiety in the 600 mg group, increase in social functioning, 47% responders in the 600 mg group (vs. 34% in the placebo group) no difference between the groups with/without APD, but greater drug/placebo difference in the comorbid group no data on drop-outs
Noyes et al. (1997) J Clin Psychopharmacol	N=583 Social phobia 62.5% generalized form 47.8% AVPD	RCT over 12 weeks	Moclobemide (RIMA) controlled dose-response trial 75–900 mg vs. placebo	No improvement independent of dose at 12 weeks (only at 8 weeks) 35% very much improved, high placebo response moderate drop-outs in both groups no difference between the groups with/without AVPD, but greater drug/placebo difference in the comorbid group
Lott et al. (1997) J Clin Psychopharmacol	N=102 Social phobia[1]	RCT over 10 weeks	Brofaromine (RIMA) 50–150 mg vs. placebo	Reduction of social anxiety, no improvement of social functioning, 50% responders (vs. 19% in the placebo group), but moderate effect moderate drop-outs in both groups
Stein et al. (1998) J Am Med Assoc	N=183 Social phobia 100% generalized form	RCT over 12 weeks	Paroxetine (SSRI) 20–50 mg vs. placebo	Reduction of social anxiety and improvement of social functioning, 55% responder (vs. 23.9% in placebo group) moderate drop-outs in both groups

Table VII (*Continued*)

Authors/Journal	Subjects	Study design	Agent/Dose	Results
Schneier et al. (1998) Br J Psychiatry	N = 77 Social phobia 85% generalized form 38% AVPD	RCT over 8 weeks	Moclobemide (RIMA) over 8 weeks 728 mg (average) vs. placebo	Reduction of two out of 10 subscores of social anxiety only (avoidance behaviour, total fear) 17.5% responder (vs. 13,5% in the placebo group), low effect moderate drop-outs in both groups
Baldwin et al. (1999) Br J Psychiatry	N = 290 Social phobia[1]	RCT over 12 weeks	Paroxetine (SSRI) 20–50 mg	Reduction of social anxiety, improvement of social functioning 65.7% responder (vs. 32.4% in placebo group) moderate drop out in both groups
Stein et al. (1999) Am J Psychiatry	N = 92 Social phobia 91.3% generalized form	RCT over 12 weeks	Fluvoxamine (SSRI) 202 mg (average) vs. placebo	Reduction of social anxiety, improvement of social functioning 42.9% responder (vs. 22.7% in placebo group) low drop-outs:
Allgulander et al. (1999) Acta Psychiatr Scan	N = 99[1]) Social phobia	RCT over 12 weeks	Paroxetine (SSRI) 20–50 mg vs. placebo	Reduction of social anxiety and improvement of social functioning 70.5% responder (vs. 8.3 in the placebo group) low drop-outs in the paroxetine group
van Ameringen et al. (2001) Am J Psychiatry	N = 204 Social phobia 100% generalized form 61% avoidant P.D.	RCT over 20 weeks	Sertraline (SSRI) 50–200 mg	Reduction of social anxiety and improvement of social functioning 53% responders (vs. 29% in the placebo group) low drop-outs in both groups
Kobak et al. (2002) J Clin Psychopharmacol	N = 60 Social phobia[1]	RCT over 14 weeks	Fluoxetine (SSRI) 20–60 mg vs. placebo	No difference between fluoxetine and placebo
Liebowitz et al. (2002) J Clin Psychiatry	N = 384 100% generalized form	RCT over 12 weeks	Paroxetine (SSRI) 20, 40 & 60 mg (fixed dose) vs. placebo	20 mg induced the greatest improvement of social anxiety, while the incidence of responders, based on the CGI was greatest for 40 mg.
Lepola et al. (2004) J Clin Psychiatry	N = 372 Social phobia[1]	RCT over 12 weeks	Paroxetine CR (controlled release) (SSRI) 12.5–37.5 mg vs. placebo	Reduction of social anxiety and improvement of social functioning responder 57% (vs. 30.4% in the placebo group) low drop-outs
Davidson et al. (2004) J Clin Psychopharmacol	N = 279 Social phobia 100% generalized form	RCT over 12 weeks	Fluvoxamine CR (controlled release) (SSRI) 100–300 mg vs. placebo	Reduction of social anxiety and improvement of social functioning
Rickels et al. (2004) J Clin Psychopharmacol	N = 272 Social phobia 100% generalized form	RCT over 12 weeks	Venlafaxine (SNRI) 75–225 mg vs. placebo	Reduction of social anxiety and improvement of social functioning

Table VII (*Continued*)

Authors/Journal	Subjects	Study design	Agent/Dose	Results
Stein et al. (2002) Arch Gen Psychiatry	$N = 257$ Social phobia 100% generalized form	RCT over 12 weeks followed by 24 weeks continuation of treatment	Paroxetine (SSRI) vs. placebo	Fewer relapse in the paroxetine compared to the placebo group (14% vs 39%)
Lader et al. (2004) Depress Anxiety	$N = 839$ Social phobia 100% generalized form	RCT over 12 weeks with continuation treatment over 24 weeks	Escitalopram (SSRI) 5, 10 & 20 mg Comparator: paroxetine 20 mg	Reduction of social anxiety and improvement of social functioning for all doses of escitalopram and for paroxetine at 24 weeks; 20 mg escitalopram superior to 20 mg paroxetine
Allgulander et al. (2004) Hum Psychopharmacol	$N = 434$ Social phobia 100% generalized form	RCT over 12 weeks Comparator:paroxetine 20–50 mg	Venlafaxine (SNRI) 75–225 mg vs. paroxetine vs. placebo	Reduction of social phobia and improvement of social functioning compared to placebo, equally efficacious to paroxetine Responders 69% in the venlafaxine, 66% in the paroxetine, and 36% in the placebo group
Kasper et al. (2005) Br J Psychiatry	$N = 358$ Social phobia 100% generalized form	RCT over 12 weeks	Escitalopram (SSRI) 10–20 mg vs. placebo	Reduction of social phobia and improvement of social functioning compared to placebo Responders 54% (vs. 39% in the placebo group)
Liebowitz et al. (2005) J Clin Psychiatry	$N = 271$ Social phobia 100% generalized form	RCT over 12 weeks	Venlafaxine (SNRI) 75–225 mg vs. placebo	Reduction of social anxiety and improvement of social functioning 44% responders (vs. 30% in the placebo group)
Liebowitz et al. (2005)	$N = 413$ Social phobia 100% generalized form	RCT over 12 weeks Comparator: paroxetine 20–50 mg (46 mg av.)	Venlafaxine (SNRI) 75–225 mg average: 201.7 mg vs. placebo	Reduction of social phobia and improvement of social functioning compared to placebo, equally efficacious to paroxetine Responders 56.6% in the venlafaxine, 62.5% in the paroxetine, and 36.1% in the placebo group
Stein et al. (2005) Psychopharmacol	$N = 386$ Social phobia 100% generalized form	RCT over 24 weeks	Venlafaxine (SNRI) 75 mg or 150–225 mg vs. placebo	Reduction of social phobia and improvement of social functioning compared to placebo under both dosages responders 58% (vs. 33% in the placebo group) improvement sustained throughout 24 weeks
Montgomery et al. (2005) J Clin Psychiatry	$N = 517$ Social phobia 100% generalized form	RCT over 24 weeks	Escitalopram (SSRI) 10–20 mg vs. placebo	Fewer relapse 22% (vs. 50% in the placebo group), low drop-outs in both groups

[1]No specification of the generalized subtype.
Low drop-outs, <15%; moderate drop-outs, 15% $<x<$ 50%; high drop-outs, $\geq$ 50%.

4.2 Treatment with antidepressants (cf. Table VII)

4.2.1 Classification and efficacy. Antidepressants have been applied for several target symptoms of social phobia: social anxiety, avoidance, low self-esteem and physiological symptoms that accompany the disorder. As the primary outcome measure, the Liebowitz Social Anxiety Scale was included in all studies, with the Sheehan Disability Inventory as a secondary outcome measure in most studies evaluating work, social and family functioning. Quite a broad database is available indicating the efficacy of SSRIs, SNRIs and MAO inhibitors (reversible and irreversible) in the treatment of generalized social phobia with, however, no RCT studies having being performed in anxious/avoidant personality disorder. The review by the Cochrane Collaboration published in 2000, which refers to 36 RCTs including 5264 patients, also comes to the conclusion that psychopharmacotherapy is efficacious in social phobia. Because of the broad database based on sufficiently large samples, the following detailed presentation is restricted to RCTs and metaanalyses.

Fifteen published RCTs of SSRIs (six on paroxetine, three on fluvoxamine, three on escitalopram, two on sertralin, one on fluoxetine) in social phobia consistently provided evidence for a high rate of success with this class of antidepressants, with most of the included patients meeting the diagnostic criteria of the generalized form (evidence level A). Response rates of the SSRIs varied between 42.9% (Stein et al. 1999) and 70.5% (Allgulander et al. 1999) compared to placebo responses of between 8.3 and 36.1%. A meta-analysis on these RCTs reported highly varying effect sizes ranging from −0.029 to 1.214 (average: 0.531) for social anxiety as measured by means of the Liebowitz Social Anxiety Scale (Hedges et al. 2006). Measurements of social functioning provided effect sizes ranging from 0.203 to 0.480 for work, 0.237 to 0.786 for social function, and 0.118 to 0.445 for family function.

Efficacy was shown to be similar with venlafaxine, indicated by five RCTs that resulted in response rates between 44 and 69% (compared to a placebo response of approximately 30%) (evidence level A). For paroxetine (Stein et al. 2002), escitalopram (Lader et al. 2004) and venlafaxine (Stein et al. 2005), improvement was sustained in the long term, at least over 6 months. Long-term effects are of particular interest in chronic conditions with early onset and chronic course. In addition, prevention potency was successfully tested for paroxetine and escitalopram, with a significant reduction of relapse rates over a 24-week observation period (Stein et al. 2001; Montgomery et al. 2005). Because of its chronic course, antidepressant therapy should be maintained at least over 12 months after response (van Ameringen et al. 2003).

The irreversible MAOI was shown to be superior to placebo in two RCTs of 16- and 12-week outcome (Versiani et al. 1992; Heimberg et al. 1998). In addition, phenelzine was shown to maintain its effects over 6 months. Therefore, data suggest that phenelzine also shows a strong benefit (evidence level B). The effects of moclobemide appear to be lower. In three RCTs including 600 mg moclobemide per day, response rates varied highly, ranging between 17.5% (Schneier et al. 1998) and 47% (Katschnig et al. 1995). In one study (Noyes et al. 1997), no superiority compared to placebo could be demonstrated. A lower dose of 300 mg/day turned out to be insufficient (Katschnig et al. 1995).

4.2.2 Comparative efficacy and tolerability. It remains to be determined how effective SSRIs are relative to other pharmacological treatments, particularly MAOIs. Therefore, direct comparisons have yet to be conducted. Nonetheless, given the demonstrated efficacies of a number of SSRIs together with their relatively benign side effect profile (nausea, dry mouth, constipation, sexual dysfunction, agitation, paraesthesia, tiredness; very low rate of severe cardiovascular and cerebrovascular adverse reactions, low rates of gastrointestinal bleeding or diabetes insipidus), SSRIs can be recommended as first-line treatment in AVPD. The studies found that substantial effects on both anxiety and avoidance behaviour were produced by increasing the turnover of neuronal serotonin, resulting in a significant improvement of social functioning.

The effects of the different SSRIs (fluvoxamine, paroxetine, escitalopram, sertraline and fluoxetine) were similar to each other, with the exception of fluoxetine, which failed to show a significant effect in the only study performed consisting of 60 subjects with social phobia (Kobak et al. 2002). Slightly more trials (five RCTs) exist for paroxetine (20–50 mg/day), while citalopram was not tested in double-blind studies for social phobia. Furthermore, one study showed a superior effect of 20 mg (but not 10 mg) escitalopram compared to 20 mg paroxetine (Lader et al. 2004); these dosages appear not to be equivalent. Further comparator studies between SSRIs are not available, and since the number of studies differs between the agents and is relatively low for any one drug, it is not possible to make reliable comparisons between individual SSRIs. With regard to the optimal treatment dose, the study provided by Liebowitz et al. (2002), which compared the effects between different dosages of paroxetine, suggests that the dose–response re-

lationship between SSRIs and treatment response in social phobia is unclear. In addition to SSRIs, the SNRI venlafaxine has been consistently shown to be effective in RCTs. Since side effects do not differ a great deal (except for noradrenergically mediated side effects such as dry mouth, constipation and high blood pressure) from those that occur during SSRI treatment, venlafaxine is a further agent recommended for first-line treatment in AVPD.

Irreversible MAOIs such as phenelzine (or tranylcypromine) were shown to be effective. However, because of the serious side effects (cf. 2.2.2), this group of antidepressants is not suitable as a first-arm treatment. They are rather standby medications for cases of non-response to other antidepressants. With regard to RIMAs, data are more inconsistent than those reported for SSRIs. This is supported by a meta-analysis, which reported response rates and effect sizes for RIMAs to be smaller than those seen for SSRIs (van der Linden et al. 2000).

4.3 Other pharmacological approaches

The anticonvulsant gabapentin and the GABA-analogue pregabalin were shown to be superior to placebo in RCTs. The study on the efficacy on gabapentin was conducted in a sample of 69 patients over 14 weeks, who received flexible doses between 900 and 3600 mg daily (Pande et al. 1999). The most frequent adverse effects were dizziness, dry mouth, somnolence, nausea, and decreased libido. Pregabalin was tested for efficacy over 10 weeks in 135 patients, only a small portion of whom fulfilled the criteria of AVPD (Pande et al. 2004). A dose of 600 mg pregabalin proved to be superior to placebo on primary and secondary measures of social phobia. Somnolence and dizziness were the most frequently occurring adverse events. No replication studies have been reported to date (evidence level D).

In addition, the β-adrenergic blocker atenolol was shown not to be superior to placebo in two 16-week RCTs including patients with social phobia (Liebowitz et al. 1990, 1992). The same is true for buspirone, which showed no significant difference to placebo in a 12-week RCT including 30 patients (van Vliet et al. 1997). Finally, the β-blocker pindolol was no more effective than placebo in augmenting the effects of SSRI (paroxetine) treatment for generalized social phobia (Stein et al. 2001).

Benzodiazepines are not recommended for treating patients with chronic forms of generalized social

Table VIII. Controlled trials on antidepressants in social phobia with an additional psychotherapy arm.

Authors/ Journal	Subjects	Study design	Agent/Dose	Results
Heimberg et al. (1998) Arch Gen Psychiatry	$N=133$ Social phobia 70.7% generalised form	CT (not randomized) over 12 weeks	Phenelzine (irrev. MAOI) 60–90 mg Comparators: pill placebo cogn.-behav. Therapy educat./support. ther.	Phenelzine and CBT better than both placebo conditions, phenelzine effect earlier; phenelzine effect on more subscores 77% responder in phenelzine, 75% in CBT group moderate drop-outs in both groups
Liebowitz et al. (1999) Depress Anxiety		Maintenance over 24 weeks and treatment-free follow-up over further 24 weeks		Relapse during maintenance treatment did not differ; in treatment-free follow-up a trend towards greater relapse in the phenelzine group
Blomhoff et al. (2001) Br J Psychiatry	$N=387$ Social phobia 100% generalized form	RCT over 24 weeks	Sertraline (SSRI) 50–150 mg Comparators: pill placebo exposure therapy exposure + sertraline	Sertraline and combined sertraline and exposure therapy superior to placebo with the combined therapy group exhibiting the best effect without significant difference to the group with sertraline alone
Davidson et al. (2004) Arch Gen Psychiatry	$N=295$ Social phobia 100% generalized form	RCT over 14 weeks	Fluoxetine (SSRI) 10–60 mg Comparators: pill placebo CBT fluoxetine+CBT	All treatments superior to placebo, at 14 weeks no difference between treatment arms, combined treatment without further advantage

phobia or AVPD because they are associated with abuse and long-term dependence.

4.4 Psychotherapy

In cognitive-behavioural therapy, the key strategy is the in vivo exposure to feared situations. Systematic desensitization (in sensu), social skills and self-assurance training programs integrating role-plays as well as cognitive restructuring and relaxation training are further well-approved interventions. At least 5 controlled studies have been performed indicating the superiority of cognitive-behavioural therapy in patients with generalized social phobia and AVPD compared to waiting list. Two meta-analyses reported effect seizes between 0.80 and 1.09 for social phobia (Harb and Heimberg 2002; Rodebaugh et al. 2004). The cognitive therapy by Clark et al. (2006) which integrates exposure plus applied relaxation even reached effect size up to 2.14. In conclusion, there seems to be a reliable evidence for the efficacy of cognitive-behavioural therapies in social phobia, although level A and even level B are difficult to apply because the studies are not randomised controlled studies but were performed against waiting-lists. Regarding the transfer of results from social phobia to AVPD, patients with AVPD are known to have more difficulties in engaging in behavioural strategies such as exposure in vivo and, on the whole, therapeutic effects seem to be smaller than in social phobia (Renneberg in press).

4.4.1 Combining pharmacotherapy with psychotherapy (cf. Table VIII).
One study compared phenelzine to cognitive-behavioural therapy in patients with social phobia, nearly two-thirds of whom met the criteria for the generalized form (Heimberg et al. 1998). The phenelzine effect began earlier and induced significant improvement on more subscales compared to cognitive-behavioural therapy. However, phenelzine showed a trend towards greater relapse in the treatment-free follow-up. Two studies tested for probable advantages of a combination therapy compared to SSRI monotherapy. Both studies failed to find a significant superiority of the combination therapy, although in one study the effect size was higher (Blomhoff et al. 2001, Davidson et al. 2004).

4.5 Treatment for children and adolescents

One RCT was performed for the acute treatment of children and adolescents with either social phobia or generalized anxiety disorder or separation anxiety disorder (Birmaher et al. 2003). In this study, which included 74 patients, fluoxetine was shown to be superior, with 61% of the patients being responders compared to 35% in the placebo group. In a further study with a very similar design, which included 128 children and adolescents, fluvoxamine was shown to be effective in 76% of the subjects compared to 29% in the placebo group (Research Units of Pediatric Psychopharmacology Anxiety Study Group 2000). Patients with adult onset of generalized social phobia exhibited better treatment response to sertraline compared to those who started in childhood or adolescence (van Ameringen et al. 2004). Further studies are needed to enable a reliable evaluation of the pharmacological potency of SSRIs or other antidepressants in children and adolescents.

Disclosure statement

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