Effectiveness of Pharmacotherapy for Severe Personality Disorders: Meta-Analyses of Randomized Controlled Trials

Theo Ingenhoven, MD; Patricia Lafay, MA; Thomas Rinne, MD, PhD; Jan Passchier, PhD; and Hugo Duivenvoorden, PhD

Context: There has been little systematic attempt to validate current pharmacologic treatment algorithms and guidelines for severe personality disorder.

Objective: We evaluated studies on the effectiveness of psychoactive drugs on specific symptom domains for borderline and/or schizotypal personality disorder.

Data sources: The literature was searched for placebo-controlled randomized clinical trials (PC-RCTs) on the effectiveness of psychopharmacologic drugs in personality disorder patients. The PubMed, PsychINFO, PiCarta, Cochrane, and Web of Science databases were searched using the search terms *borderline personality*, *schizotypal personality*, *personality disorder*, *cluster A*, *cluster B*, *treatment*, *drug*, *pharmacotherapy*, *antipsychotic*, *antidepressant*, *mood stabilizer*, *effect*, *outcome*, *review*, and *meta-analysis* for studies published between 1980 and December 2007, and references were identified from bibliographies from articles and books.

Study selection: Placebo-controlled randomized clinical trials on the efficacy of antipsychotics, antidepressants, and mood stabilizers regarding cognitive-perceptual symptoms, impulsive-behavioral dyscontrol, and affective dysregulation (with subdomains depressed mood, anxiety, anger, and mood lability) were selected in patients with well defined borderline and/or schizotypal personality disorder. Studies whose primary emphasis was on the treatment of Axis I disorders were excluded. Meta-analyses were conducted using 21 retrieved studies.

Results: Antipsychotics have a moderate effect on cognitive-perceptual symptoms (5 PC-RCTs; standardized mean difference [SMD] = 0.56) and a moderate to large effect on anger (4 PC-RCTs; SMD = 0.69). Antidepressants have no significant effect on impulsive-behavioral dyscontrol and depressed mood. They have a small but significant effect on anxiety (5 PC-RCTs; SMD = 0.30) and anger (4 PC-RCTs; SMD = 0.34). Mood stabilizers have a very large effect on impulsive-behavioral dyscontrol (6 PC-RCTs; SMD = 1.51) and anger (7 PC-RCTs; SMD = 1.33), a large effect on anxiety (3 PC-RCTs; SMD = 0.80), but a moderate effect on depressed mood (5 PC-RCTs; SMD = 0.55). Mood lability as an outcome measure was seldomly assessed. Mood stabilizers have a more pronounced effect on global functioning (3 PC-RCTs; SMD = 0.79) than have antipsychotics (5 PC-RCTs; SMD = 0.37). The effect of antidepressants on global functioning is negligible.

Conclusions: Drug therapy tailored to well-defined symptom domains can have a beneficial effect on patients with severe personality disorder. The findings from this study raise questions on current pharmacologic algorithms.

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Corresponding author: *Theo Ingenhoven, MD, Symfora Group, Postbox 3051, 3800DB Amersfoort, The Netherlands (tjm.ingenhoven@symfora.nl).*

There is a growing consensus that severe personality disorders can be described as syndromes of interacting traits, originating from biologic predispositions and/or psychosocial function.[1] Furthermore, some personality dimensions are mediated by deregulation of the neurotransmitter system. Current treatment algorithms are based on the presumption that drugs will remedy both the symptoms during episodes of (acute) decompensation and the biologic vulnerabilities. By targeting the neurotransmitter physiology that regulates cognition, perception, impulse, and affect, pharmacotherapy may modify these manifestations, and thereby enable significant relearning in interpersonal behavior. In Soloff's view,[2,3] pharmacotherapy is best seen as an adjunctive treatment aimed at stabilizing symptoms and behavior, thereby facilitating psychosocial interventions to develop adaptive coping skills, interpersonal functioning, and reflective capacities.

This psychobiological model tailors pharmacotherapy for severe personality disorder patients to 3 symptom domains. The first is the domain of cognitive-perceptual symptoms, ie, suspiciousness, referential thinking, paranoid ideation, illusions, derealization, depersonalization, and hallucination-like symptoms. The second domain is that of impulsive-behavioral dyscontrol, ie, impulsive aggression, self-mutilation, promiscuous sex, substance abuse, and reckless spending. Third, there is the domain of affective dysregulation, ie, mood lability, rejection sensitivity,

inappropriateness of intense anger, depressive mood crashes, and outbursts of temper. Treatment recommendations with minor modifications based on Soloff's systematic reviews form the basis of the *Practice Guideline for the Treatment of Patients with Borderline Personality Disorder*.[4]

Recent reviews indicate that results of studies on pharmacotherapy in personality disorders are still inconsistent, partly to be ascribed to serious methodological flaws and to missing or failed replications.[5] Results are assessed by a multifacetedness of measurement instruments covering more or less similar symptom domains. The answer to the question of whether overriding conclusions can be drawn should come from meta-analysis. Two meta-analyses on pharmacologic trials in patients with borderline personality disorder (BPD) have been published.[6,7] One is from the Cochrane Collaboration[6] and includes a limited number of randomized controlled trials (RCTs) on predominantly classic antipsychotics, tricyclic antidepressants, and monoamine oxidase (MAO) inhibitors published between 1980 and 2001. Studies involving atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs) or comparable modern antidepressants, and mood stabilizers were scarce at that time. The study did not find good evidence for pharmacologic effectiveness in patients with BPD. The second, a meta-analysis by Nose et al[7] on RCTs published before June 2006 concluded that antidepressants and mood stabilizers are effective against mood lability and anger, but not against impulsivity and aggression, unstable relations, suicidality, and global functioning. The reverse was true for antipsychotics, as they have a positive effect on impulsivity and aggression, interpersonal relationships, and global functioning. Regrettably, these 2 meta-analyses differ on inclusion criteria, clustering of psychoactive drugs into clinically useful categories, and their focus on clinically relevant symptom domains.

The primary objective of the present study was to address these issues by clarifying the effect sizes of antipsychotics, antidepressants, and mood stabilizers on specific symptom domains in patients with severe personality disorder. To this aim, we analyzed double-blind, placebo-controlled randomized clinical trials (PC-RCTs) on drug effectiveness in patients with a well-defined diagnosis of BPD and/or schizotypal personality disorder (StPD), without a major emphasis on Axis I psychopathology. In contrast to earlier meta-analyses, we classified all relevant compatible outcome variables into the domains of cognitive-perceptual symptoms, impulsive-behavioral dyscontrol, and affective dysregulation subdomains (depressed mood, anxiety, anger, and mood lability).

METHOD

Data Sources and Study Selection

The PubMed, PsychINFO, PiCarta, Cochrane, and Web of Science databases were searched for publications between 1980 and December 2007 on the effect of psychotropic medication in adult personality-disordered patients as defined by *DSM-III*, *DSM-III-R*, or *DSM-IV*. The following search terms were used: *borderline personality*, *schizotypal personality*, *personality disorder*, *cluster A*, *cluster B*, *treatment*, *drug*, *pharmacotherapy*, *antipsychotic*, *antidepressant*, *mood stabilizer*, *effect*, *outcome*, *review*, and *meta-analysis*. Reference lists of relevant publications were searched manually for additional references. Eligible publications were selected by applying the inclusion and exclusion criteria specified for study population, interventions, study design, outcome variables, methodology, and results.

Inclusion and Exclusion of Studies

Only PC-RCTs studying pharmacotherapy in well-defined BPD and StPD as assessed by a validated semistructured interview based on *DSM-III* and beyond were selected. If more than 1 article reported results from the same study population, only 1 was selected to avoid duplication. Placebo-controlled randomized clinical trials studying pharmacotherapy in other *DSM* personality disorders were excluded, as were those with a primary focus on the treatment of a comorbid Axis I disorder, such as psychotic, affective, or anxiety disorders.

Outcome Measures

Outcome variables were classified into 3 symptom domains: cognitive-perceptual symptoms, impulsive-behavioral dyscontrol, and affective dysregulation.[2–4] The latter domain was subdivided into 4 subdomains: depressed mood, anxiety, anger, and mood lability.[5] Moreover, global functioning was added as an outcome measure. Three of the authors (T.I., P.L., H.D.) assigned the measurement instruments used, and every subscale involved, to these 7 (sub)domains whenever possible. If a measurement instrument could not be assigned properly, it was eliminated from analysis.

Data Extraction

The same authors (T.I., P.L., H.D.) extracted data onto a standard form. Any differences were resolved in consensus. The following data were recorded: authors and year of publication, the semistructured interview used for diagnosing personality disorders, inpatient or outpatient status, gender, numbers of subjects using active drug or placebo, dosage of active agent, treatment duration, intention-to-treat analysis, patient dropout rates, and outcome variables. For continuous outcome measures, the group mean scores at start and end point as well as accompanying standard deviation (SD) or standard error (SE) were recorded. If applicable, SE was converted into SD.[8] When outcomes were not fully reported, we requested additional data from the first author of the study. If not provided eventually, we intended to calculate the SDs on the basis of other studies using the same drug and outcome variables.[9]

Data Analysis

For each study, the standardized mean differences (SMDs) between the groups using active agents and placebo control were calculated using Cohen's *d*.[10] Effect sizes were corrected for small sample size.[11] Overall differences were obtained by pooling the individual study differences by means of a fixed-effects model and, if appropriate, a random-effects model.[12] A fixed-effects model considers the variability between studies' results as random variation by weighing the precision of the individual studies. The validity of this assumption was tested using a χ^2 test, under the null hypothesis that the effects of the individual studies were homogeneous. If, however, this assumption was violated ($P < .05$, 2-tailed), a random-effects model was applied. We tested for homogeneity with the Cochran Q test. In addition, I^2 served as a measure of degree of heterogeneity, being the percentage of total variance across studies attributable to heterogeneity. I^2 up to 25% reflects low heterogeneity; from 25% up to 50%, moderate heterogeneity; and more than 50%, high heterogeneity.[13] Effect sizes of the meta-analyses are presented as pooled SMDs and their 95% confidence intervals (CIs). Data were analyzed using Microsoft Excel 2000 (Microsoft Corporation, Redmond, Washington). For all analyses, an α value of .05 (2-tailed) was considered statistically significant.

RESULTS

Study Selection

The search strategy and study selection resulted in 35 PC-RCTs on pharmacotherapy for BPD and/or StPD. Eleven PC-RCTs studied antipsychotics; 11, antidepressants; and 10, mood stabilizers. Three of the 35 PC-RCTs studied other drugs: alprazolam,[14] omega-3 fatty acids,[15] and naloxone.[16] (For a narrative review of these PC-RCTs, see Rinne and Ingenhoven.[5]) The latter 3 were excluded from analysis, leaving 32 studies (Table 1). However, 11 of these, published in 7 articles, could not be included in the meta-analyses because of study flaws. Flaws were the following: absence of placebo control in second arm within the crossover design, with trifluoperazine and phenelzine in the study by Cowdry and Gardner[14] and desipramine in the study by Links et al[17]; follow-up design[18]; no continuous outcome variables[17,19]; and lack of relevant data to estimate an appropriate pooled effect size.[20–22] Paul Markovitz kindly provided additional data for 1 study.[23] For lack of comparative studies using the same outcome measures for calculating missing data, using the strategy of Furukawa et al[9] was not possible in the study by Goldberg et al.[20] Thus, 21 PC-RCTs, published in 19 articles, were finally subjected to meta-analyses (Table 1).

Antipsychotics

All patients in the 6 selected randomized trials met the criteria for BPD and/or StPD, without specific major Axis I psychotic disorder. The studies by Soloff et al[24,25] included borderline inpatients, about 60% of whom were diagnosed as having comorbid schizotypal traits or StPD. The study by Koenigsberg et al[26] in an outpatient setting primarily focused on StPD. In all studies, both sexes were eligible. A total number of 144 patients received a classic or atypical antipsychotic drug versus 140 patients on placebo medication. The mean attrition rate was 30%. At end point, numbers of participating patients per study varied from 23[26] to 60.[27]

Cognitive-perceptual symptoms. In 5 studies,[24–26,28,29] cognitive-perceptual symptoms were assessed by the subscales transient paranoia and dissociation of the Clinical Global Impressions modified for borderline personality disorder (CGI-BPD), the Schizotypal Symptom Inventory, the Schizotypal Personality Questionnaire, the positive scale of the Positive and Negative Syndrome Scale, the subscale paranoid of the Inpatient Multidimensional Psychiatric Scale (IMPS) and the subscales paranoid and psychoticism of the Symptom Checklist-90 (SCL-90). Mean effect sizes (SMD) varied from SMD = −0.04[25] to SMD = 1.23[26] (Table 2). Analysis of homogeneity indicated significantly different results of the studies ($I^2 = 70\%$), which called for a random-effect meta-analysis. The pooled effect size of antipsychotics on cognitive-perceptual symptoms (SMD = 0.56; 95% CI, 0.05–1.07) was significant ($P < .05$) and was qualified as moderate.[10]

Impulsive-behavioral dyscontrol. In 5 studies,[24,25,27–29] impulsive-behavioral dyscontrol was assessed by the subscales impulsivity and recurrent suicidality of the CGI-BPD, the subscales anger-out and anger control of the State-Trait Anger Expression Inventory (STAXI), behavior reports (impulsivity, self-injuring, and emergency room visits), the Ward Scale of Impulse Action Patterns (WSIAP), Barratt Impulsiveness Scale, version II (BIS), Self-Report Test of Impulse Control (STIC), and Buss-Durkee Hostility Inventory (BDHI). Mean effect sizes, corrected for small sample size, varied from SMD = −0.09[27] to SMD = 1.25[29] per study (Table 2). As I^2 was 73%, a random-effect meta-analysis was performed. The pooled effect size of antipsychotics on impulsive-behavioral dyscontrol was not significant (SMD = 0.26; 95% CI, −0.21 to 0.74). This means that antipsychotics did not affect impulsive-behavioral dyscontrol.

Affective dysregulation. Depressed mood. In 5 studies,[24–27,29] depressed mood was assessed by the Beck Depression Inventory (BDI), Hamilton Depression Inventory (HDI), 17- and 24-item Hamilton Depression Rating Scales (HDRS-17 and HDRS-24), the subscale depression of the SCL-90, and the subscale intrapunitiveness of the IMPS. Mean effect sizes varied from SMD = −0.45[25] to SMD = 1.60.[29] (Table 2). As I^2 was 85%, a random-effect meta-analysis was performed. The pooled effect size of antipsychotics on depressed mood was not significant (SMD = 0.46; 95% CI, −0.21 to 1.14).

Anxiety. In 4 studies,[24,25,27,29] anxiety was assessed by the Hamilton Anxiety Rating Scale (HARS) and the

Table 1. Placebo-Controlled Randomized Clinical Trials (PC-RCTs) in Severe Personality Disorder: Study Characteristics, Participants, and Coverage of Outcome Domains

PC-RCT	Medication: Active Drug	Medication: Daily Dose	Patients: Included, N (% dropout[a])	Patients: Gender	Design: Setting	Design: Duration, Wk	Target Domains for Meta-Analysis: Cognitive-Perceptual Symptoms	Impulsive-Behavioral Dyscontrol	Affective Dysregulation: Depressed Mood	Affective Dysregulation: Anxiety	Affective Dysregulation: Anger	Affective Dysregulation: Mood Lability	Global Functioning
Antipsychotics													
Montgomery and Montgomery[19] (1982)[b]	Flupentixol (intramuscular)	20 mg/4wk	30[c]	Male/female	Inpatient/ outpatient	24		■					
Goldberg et al[20] (1986)[b]	Thiotixene	8.7 mg	50 (48)	Male/female	Outpatient	12	■		□	■			□
Cowdry and Gardner[14] (1988)[b]	Trifluoperazine	7.8 mg	23 (57)	Female	Outpatient	6		■□	□	■	□		□
Soloff et al[24] (1989)	Haloperidol	4–16 mg	60 (7)	Male/female	Inpatient	6	■	■	■	□	■		■
Soloff et al[25] (1993)	Haloperidol	4 mg	70 (17)	Male/female	Inpatient	5	□	□	□	□	□		□
Cornelius et al[18] (1993)[b]	Haloperidol	≤6 mg	32 (25)	Male/female	Outpatient	16	□	■	□		□		
Zanarini and Frankenburg[22] (2001)[b]	Olanzapine	5.3 mg	28 (50)	Female	Outpatient	26	■		□	■	■		
Koenigsberg et al[26] (2003)	Risperidone	0.25–2 mg	25 (48)	Male/female	Outpatient	9	■		□				□
Bogenschutz and Nurnberg[28] (2004)	Olanzapine	2.5–20 mg	40 (43)	Male/female	Outpatient	12	□	□	□		■□	□	□
Soler et al[27] (2005)	Olanzapine	5–20 mg	60 (30)	Male/female	Outpatient	16		■□	■	■			□
Nickel et al[29] (2006)	Aripiprazole	15 mg	52 (10)	Male/female	Outpatient	8	■	■	■	■	■		■
Antidepressants													
Montgomery and Montgomery[19] (1982)[b]	Mianserine	30 mg	38[b]	Male/female	Inpatient/ outpatient	24		□					
Cowdry and Gardner[14] (1988)[b]	Tranylcypromine	40 mg	25 (44)	Female	Outpatient	6		■□	■	■	■□		■
Soloff et al[24] (1989)	Amitriptyline	100–175 mg	59 (3)	Male/female	Inpatient	6	□	□	■	□	■		□
Links et al[17] (1990)[b]	Desipramine	163 mg	25 (32)	Male/female	Inpatient/ outpatient	6		□	□		□		□
Soloff et al[25] (1993)	Phenelzine	60 mg	72 (14)	Male/female	Inpatient	5	□	□	□	□	■		□
Cornelius et al[18] (1993)[b]	Phenelzine	≤90 mg	40 (23)	Male/female	Outpatient	16		■	□				
Salzman et al[33] (1995)	Fluoxetine	40 mg	27 (19)	Male/female	Outpatient	12		□	■		■		
Markovitz[23] (1995)	Fluoxetine	80 mg	17 (18)	Male/female	Inpatient/ outpatient	14			■	■			■
Coccaro and Kavoussi[32] (1997)	Fluoxetine	20–60 mg	40 (35)	Male/female	Outpatient	13		■	□	■	■		
Rinne et al[30] (2002)	Fluvoxamine	150 mg	38 (8)	Female	Outpatient	6		□				■	
Simpson et al[31] (2004)	Fluoxetine	Max 40 mg	25 (20)	Male/female	Inpatient/ outpatient	12	□	□	□	□			□
Mood stabilizers													
Cowdry and Gardner[14] (1988)	Carbamazepine	820 mg	28 (46)	Female	Outpatient	6		■□	■□	■□	■□		■
Links et al[17] (1990)[b]	Lithium	986 mg	24 (33)	Male/female	Inpatient/ outpatient	6		■	□		□		■
De la Fuente and Lotstra[35] (1994)	Carbamazepine	Plasma level	20 (10)	Male/female	Inpatient	5	□		■□	□	□		□
Hollander et al[36] (2001)	Valproate	Plasma level	16 (63)	Male/female	Outpatient	10		□	□				■
Frankenburg and Zanarini[34] (2002)	Valproate	500 mg	30 (63)	Female	Outpatient	26		■	□		■		
Hollander et al[21] (2003)[b]	Valproate	Plasma level	91 (9)	Male/female	Outpatient	12		■			■		
Nickel et al[38] (2004)	Topiramate	50–250 mg	31 (6)	Female	Outpatient	8		■			■		
Tritt et al[37] (2005)	Lamotrigine	50–200 mg	27 (11)	Female	Outpatient	8		■			■		
Nickel et al[40] (2005)	Topiramate	50–250 mg	44 (5)	Male	Outpatient	8		■			■		
Loew et al[39] (2006)	Topiramate	25–200 mg	56 (7)	Female	Outpatient	10	□		□	■	■		■

[a]Patients who did not complete final outcome measures.
[b]Study not included in meta-analyses.
[c]Dropout rate not specified in study.
Symbols: ■ = Domain in study, with statistically significant positive result compared to placebo control within study; □ = domain in study, with statistically nonsignificant result compared with placebo control within study; ■□ = domain in study, with equivocal or contradictory statistical results on different outcome instruments within study.

Table 2. Meta-Analyses of Antipsychotics in Randomized Controlled Trials (RCTs)

		Individual Studies				Homogeneity Analysis					Meta-Analysis Results		
RCT per Domain	Drug	Active Drug, n	Placebo, n	Standardized Mean Difference[a]	SE	Cochran Q Test	I^2 (%)[b]	*df*	*P* Value	Type	Pooled Standardized Mean Difference	95% CI	*P* Value
Cognitive-perceptual symptoms													
Soloff et al[24] (1989)	Haloperidol	28	28	0.62	0.28	13.33	70	4	<.05	Random	0.56	0.05 to 1.07	.03
Soloff et al[25] (1993)	Haloperidol	30	28	−0.04	0.26								
Koenigsberg et al[26] (2003)	Risperidone	14	9	1.23	0.46								
Bogenschutz and Nurnberg[28] (2004)	Olanzapine	16	19	0.04	0.34								
Nickel et al[29] (2006)	Aripiprazole	26	26	1.13	0.30								
Impulsive-behavioral dyscontrol													
Soloff et al[24] (1989)	Haloperidol	28	28	0.19	0.27	14.58	73	4	<.05	Random	0.26	−0.21 to 0.74	.29
Soloff et al[25] (1993)	Haloperidol	30	28	0.06	0.26								
Bogenschutz and Nurnberg[28] (2004)	Olanzapine	16	19	−0.08	0.34								
Soler et al[27] (2005)	Olanzapine	30	30	−0.09	0.26								
Nickel et al[29] (2006)	Aripiprazole	26	26	1.25	0.30								
Affective dysregulation													
Depressed mood													
Soloff et al[24] (1989)	Haloperidol	28	28	0.42	0.27	26.72	85	4	<.05	Random	0.46	−0.21 to 1.14	.18
Soloff et al[25] (1993)	Haloperidol	30	28	−0.45	0.26								
Koenigsberg et al[26] (2003)	Risperidone	14	9	0.44	0.44								
Soler et al[27] (2005)	Olanzapine	30	30	0.35	0.26								
Nickel et al[29] (2006)	Aripiprazole	26	26	1.60	0.30								
Anxiety													
Soloff et al[24] (1989)	Haloperidol	28	28	0.30	0.27	10.28	71	3	<.05	Random	0.23	−0.26 to 0.72	.36
Soloff et al[25] (1993)	Haloperidol	30	28	−0.40	0.26								
Soler et al[27] (2005)	Olanzapine	30	30	0.23	0.26								
Nickel et al[29] (2006)	Aripiprazole	26	26	0.83	0.29								
Anger													
Soloff et al[24] (1989)	Haloperidol	28	28	0.47	0.27	10.05	70	3	<.05	Random	0.69	0.16 to 1.22	.02
Soloff et al[25] (1993)	Haloperidol	30	28	0.23	0.27								
Bogenschutz and Nurnberg[28] (2004)	Olanzapine	16	19	0.65	0.35								
Nickel et al[29] (2006)	Aripiprazole	26	26	1.45	0.30								
Global functioning													
Soloff et al[24] (1989)	Haloperidol	28	28	0.52	0.28	18.74	79	4	<.05	Random	0.37	0.12 to 0.62	.01
Soloff et al[25] (1993)	Haloperidol	30	28	−0.27	0.26								
Koenigsberg et al[26] (2003)	Risperidone	14	9	0.92	0.45								
Soler et al[27] (2005)	Olanzapine	30	30	0.03	0.26								
Nickel et al[29] (2006)	Aripiprazole	26	26	1.27	0.30								

[a]Corrected for small sample size.
[b]Higgins heterogeneity quantity.

subscales obsessive-compulsive, anxiety, and phobic anxiety of the SCL-90. Mean effect sizes per study varied from SMD = −0.40[25] to SMD = 0.83[29] (Table 2). The pooled effect size of antipsychotics on anxiety was not significant (SMD = 0.23; 95% CI, −0.26 to 0.72), as it appeared from a random-effect meta-analysis with $I^2 = 71\%$.

Anger. In 4 studies,[24,25,28,29] anger was assessed by the subscale appropriate anger of the CGI-BPD, the subscales state anger, trait anger, and anger-in of the STAXI, the subscale hostility of the SCL-90, the subscale indirect of the BDHI, and the subscales excitement and hostile belligerence of the IMPS. For the subsequent studies, the mean effect sizes (Table 2) varied from SMD = 0.23[25] to SMD = 1.45.[29] As I^2 was 70%, a random-effect meta-analysis was performed. The pooled effect size of antipsychotics on anger (SMD = 0.69; 95% CI, 0.16–1.22) was significant ($P < .05$) and was qualified as moderate to large.[10]

Mood lability. Only 1 of the studies explored the effect of antipsychotics on mood lability in borderline patients.[28] Affective instability was assessed by CGI-BPD. The effect size (SMD = 0.41; 95% CI, −0.27 to 1.09) was not significant. Applying meta-analysis was not relevant.

Global functioning. In 5 studies,[24–27,29] global functioning was assessed by the Global Severity Index, SCL-90 and the Global Assessment Scale (GAS). For the individual studies, mean effect sizes corrected for small sample size ranged from SMD = −0.27[25] to SMD = 1.27[29] (Table 2). As I^2 was 79%, a random-effect meta-analysis was performed. The pooled effect size of antipsychotics on global functioning (SMD = 0.37; 95% CI, 0.12–0.62) was significant ($P < .01$) and was qualified as small to moderate.[10]

Antidepressants

All patients included in the selected randomized trials met the criteria for BPD. Studies did not focus on the treatment of major affective disorders, anxiety disorders, or other Axis I disorders. In Soloff's studies,[24,25] about 60% of the participants were diagnosed as also having comorbid schizotypal traits or StPD. These studies both comprised inpatients; the other studies included only borderline outpatients. Rinne and colleagues[30] studied only female patients. In Soloff's studies, both sexes were eligible. A total of 133 patients received antidepressants versus 110 patients on placebo medication. At end point, the number of participating patients per study varied from 14[23] to 62.[25] The mean attrition rate was 19%, which is significantly less than in the antipsychotics studies (χ^2 test, $P < .01$).

Cognitive-perceptual symptoms. In 3 studies,[24,25,31] cognitive-perceptual symptoms were assessed by the Dissociative Experience Scale, Schizotypal Symptom Inventory, the subscale paranoid of the IMPS, and the subscales paranoid and psychoticism of the SCL-90. Mean effect sizes for the individual studies varied from SMD = −0.42[31] to SMD = 0.26[25] (Table 3). As I^2 was 0%, a fixed-effect meta-analysis was performed. The pooled effect size of antidepressants on cognitive-perceptual symptoms (SMD = 0.11; 95% CI, −0.22 to 0.45) was not significant.

Impulsive-behavioral dyscontrol. In 5 studies,[24,25,30–32] impulsive-behavioral dyscontrol was assessed by the subscale aggression of the Anger, Irritability, and Assault Questionnaire; the subscales anger and impulsivity of the Borderline Personality Disorder Severity Index (BPDSI); the subscale suicidality of the Overt Aggression Scale-Modified (OAS-M); WSIAP; BIS; STIC; and BDHI. Mean effect sizes varied from SMD = −0.44[31] to SMD = 0.61[32] (Table 3). Again, a fixed-effect meta-analysis was appropriate since I^2 was 0%. The pooled effect size of antidepressants on impulsive-behavioral dyscontrol (SMD = 0.10; 95% CI, −0.17 to 0.37) was not significant.

Affective dysregulation. Depressed mood. In 6 studies,[23–25,31–33] depressed mood was assessed by the HDRS-21, BDI, HDRS-17, HDRS-24, the subscale depression of the SCL-90, the subscale intrapunitiveness of the IMPS, HDI, and the subscale depression of the Profile of Mood States. Mean effect sizes for the individual studies varied from SMD = −0.76[31] to SMD = 1.15[23] (Table 3). As I^2 was 49%, a random-effect meta-analysis was performed. The pooled effect size of antidepressants on depressed mood was not significant (SMD = 0.29; 95% CI, −0.15 to 0.72), indicating that antidepressants have a negligible effect on depressed mood in the absence of a major affective disorder.

Anxiety. In 5 studies,[23–25,31,32] anxiety was assessed by the HARS, HARS-14, the State-Trait Anxiety Inventory, and subscales obsessive compulsive, anxiety, and phobic anxiety of the SCL-90. Mean effect sizes varied from SMD = −0.15[31] to SMD = 0.92[23] (Table 3). As I^2 was 0%, a fixed-effect meta-analysis was performed. Although significant ($P < .05$), the pooled effect size of antidepressants on anxiety (SMD = 0.30; 95% CI, 0.02–0.59) was qualified as small to moderate.[10]

Anger. In 4 studies,[24,25,32,33] anger was assessed by the subscale irritability of the Anger, Irritability, and Assault Questionnaire; the subscale hostility of the SCL-90; the subscale indirect of the BDHI; and the subscales excitement and hostile belligerence of the IMPS; the Personality Disorder Rating Scale; and the subscale anger of the Profile of Mood States. For individual studies, the mean effect sizes varied from SMD = 0.21[25] to SMD = 0.69[32] (Table 3). As I^2 was 0%, a fixed-effect meta-analysis was performed. Again, the pooled effect size of antidepressants (SMD = 0.34; 95% CI, 0.03–0.65) was significant ($P < .05$), but the magnitude of the effect was qualified as small to moderate.[10]

Mood lability. Only 1 of the studies explored the effect of antidepressants on mood lability in borderline patients.[30] Rapid mood shifts were assessed by the BPDSI. The effect size of this individual study (SMD = 0.64; 95% CI, −0.02 to 1.31) was nonsignificant. Applying meta-analysis was not relevant.

Global functioning. In 4 studies,[23–25,31] global functioning was assessed by the SCL-90, GAS, and the GAF. Mean effect sizes varied from SMD = 0.06[31] to SMD = 0.85[23] (Table 3). As

Table 3. Meta-Analyses of Antidepressants in Randomized Controlled Trials (RCTs)

		Individual Studies				Homogeneity Analysis					Meta-Analysis Results		
RCT per Domain	Drug	Active Drug, n	Placebo, n	Standardized Mean Difference[a]	SE	Cochran Q Test	I^2 (%)[b]	*df*	*P* Value	Type	Pooled Standardized Mean Difference	95% CI	*P* Value
Cognitive-perceptual symptoms													
Soloff et al[24] (1989)	Amitriptyline	29	28	0.17	0.27	1.85	0	2	NS	Fixed	0.11	−0.22 to 0.45	.51
Soloff et al[25] (1993)	Phenelzine	34	28	0.26	0.26								
Simpson et al[31] (2004)	Fluoxetine	9	11	−0.42	0.44								
Impulsive-behavioral dyscontrol													
Soloff et al[24] (1989)	Amitriptyline	29	28	0.05	0.27	3.91	0	4	NS	Fixed	0.10	−0.17 to 0.37	.50
Soloff et al[25] (1993)	Phenelzine	34	28	0.00	0.26								
Coccaro and Kavoussi[32] (1997)	Fluoxetine	27	13	0.61	0.35								
Rinne et al[30] (2002)	Fluvoxamine	20	18	0.21	0.33								
Simpson et al[31] (2004)	Fluoxetine	9	11	−0.44	0.44								
Affective dysregulation													
Depressed mood													
Soloff et al[24] (1989)	Amitriptyline	29	28	0.44	0.27	9.75	49	5	<.05	Random	0.29	−0.15 to 0.72	.20
Soloff et al[25] (1993)	Phenelzine	34	28	0.20	0.26								
Salzman et al[33] (1995)	Fluoxetine	7[c]	5[c]	0.45	0.60								
Markovitz[23] (1995)	Fluoxetine	7	7	1.15	0.48								
Coccaro and Kavoussi[32] (1997)	Fluoxetine	27	13	0.37	0.34								
Simpson et al[31] (2004)	Fluoxetine	9	11	−0.76	0.43								
Anxiety													
Soloff et al[24] (1989)	Amitriptyline	29	28	0.22	0.27	3.90	0	4	NS	Fixed	0.30	0.02 to 0.59	.04
Soloff et al[25] (1993)	Phenelzine	34	28	0.18	0.26								
Markovitz[23] (1995)	Fluoxetine	7	7	0.92	0.47								
Coccaro and Kavoussi[32] (1997)	Fluoxetine	27	13	0.62	0.35								
Simpson et al[31] (2004)	Fluoxetine	9	11	−0.15	0.45								
Anger													
Soloff et al[24] (1989)	Amitriptyline	29	28	0.25	0.27	1.36	0	3	NS	Fixed	0.34	0.03 to 0.65	.04
Soloff et al[25] (1993)	Phenelzine	34	28	0.21	0.26								
Salzman et al[33] (1995)	Fluoxetine	7[c]	5[c]	0.41	0.60								
Coccaro and Kavoussi[32] (1997)	Fluoxetine	27	13	0.69	0.35								
Global functioning													
Soloff et al[24] (1989)	Amitriptyline	29	28	0.31	0.27	1.41	0	3	NS	Fixed	0.22	−0.12 to 0.55	.21
Soloff et al[25] (1993)	Phenelzine	34	28	0.18	0.26								
Simpson et al[31] (2004)	Fluoxetine	9	11	0.06	0.45								
Markovitz[23] (1995)	Fluoxetine	7	7	0.85	0.56								

[a]Corrected for small sample size.
[b]Higgins heterogeneity quantity.
[c]Number reduced to 50% based on the percentage of sample with borderline personality disorder.
Abbreviation: NS = not statistically significant.

Table 4. Meta-Analyses of Mood Stabilizers in Randomized Controlled Trials (RCTs)

		Individual Studies				Homogeneity Analysis					Meta-Analysis Results		
RCT per Domain	Drug	Active Drug, n	Placebo, n	Standardized Mean Difference[a]	SE	Cochran Q test	I^2 (%)[b]	*df*	*P* Value	Type	Pooled Standardized Mean Difference	95% CI	*P* Value
Cognitive-perceptual symptoms													
de la Fuente and Lotstra[35] (1994)	Carbamazepine	8	10	0.42	0.49	0.00	0	1	NS	Fixed	0.42	−0.05 to 0.89	.09
Loew et al[39] (2006)	Topiramate	28	28	0.42	0.27								
Impulsive-behavioral dyscontrol													
Cowdry and Gardner[14] (1988)	Carbamazepine	15	13	0.62	0.43	49.01	90	5	< .05	Random	1.51	0.42 to 2.59	.01
Hollander et al[36] (2001)	Valproate	12	4	0.54	0.59								
Frankenburg and Zanarini[34] (2002)	Valproate	20	10	0.30	0.39								
Nickel et al[38] (2004)	Topiramate	19	10	2.86	0.45								
Tritt et al[37] (2004)	Lamotrigine	18	9	1.32	0.44								
Nickel et al[40] (2005)	Topiramate	22	20	3.30	0.37								
Affective dysregulation													
Depressed mood													
Cowdry and Gardner[14] (1988)	Carbamazepine	15	13	0.45	0.43	0.83	0	4	NS	Fixed	0.55	0.21 to 0.90	.01
de la Fuente and Lotstra[35] (1994)	Carbamazepine	8	10	0.58	0.49								
Hollander et al[36] (2001)	Valproate	12	4	1.07	0.61								
Frankenburg and Zanarini[34] (2002)	Valproate	20	10	0.49	0.40								
Loew et al[39] (2006)	Topiramate	28	28	0.51	0.28								
Anxiety													
Cowdry and Gardner[14] (1988)	Carbamazepine	15	13	0.95	0.44	0.69	0	2	NS	Fixed	0.80	0.38 to 1.21	.001
de la Fuente and Lotstra[35] (1994)	Carbamazepine	8	10	0.44	0.49								
Loew et al[39] (2006)	Topiramate	28	28	0.85	0.28								
Anger													
Cowdry and Gardner[14] (1988)	Carbamazepine	15	13	0.36	0.43	55.30	89	6	< .05	Random	1.33	0.43 to 2.22	.01
de la Fuente and Lotstra[35] (1994)	Carbamazepine	8	10	0.34	0.48								
Frankenburg and Zanarini[34] (2002)	Valproate	20	10	0.15	0.39								
Nickel et al[38] (2004)	Topiramate	19	10	2.35	0.44								
Nickel et al[40] (2005)	Topiramate	22	20	1.20	0.33								
Tritt et al[37] (2005)	Lamotrigine	18	9	1.69	0.44								
Loew et al[39] (2006)	Topiramate	28	28	3.10	0.31								
Global functioning													
Cowdry and Gardner[14] (1988)	Carbamazepine	15	13	0.92	0.40	0.62	0	2	NS	Fixed	0.79	0.38 to 1.19	.001
de la Fuente and Lotstra[35] (1994)	Carbamazepine	8	10	0.45	0.49								
Loew et al[39] (2006)	Topiramate	28	28	0.83	0.28								

[a]Corrected for small sample size.
[b]Higgins heterogeneity quantity.
Abbreviation: NS = not statistically significant.

I^2 was 0%, a fixed-effect meta-analysis was performed. The pooled effect size of antidepressants on global functioning was not significant (SMD = 0.22; 95% CI, −0.12 to 0.55).

Mood Stabilizers

In the study by Frankenburg and Zanarini,[34] all borderline patients had a comorbid bipolar II disorder. However, this study did not focus primarily on stabilization of mood but rather on impulsive behavior and anger. All remaining studies included borderline patients without specific comorbid Axis I disorder. The participants in the studies by de la Fuente and Lofstra[35] were inpatients; all other studies included outpatients only. Two studies[35,36] included both sexes, 5 studies[14,34,37–39] included female patients only, and 1 study[40] included males only. A total of 142 patients received a mood stabilizer versus 104 patients on placebo medication. At end point, the number of participating patients per study varied from 16[36] to 56.[39] The mean attrition rate was 19%, which is significantly less than it was in the antipsychotics studies (χ^2 test, $P < .01$).

Cognitive-perceptual symptoms. In 2 studies,[35,39] cognitive-perceptual symptoms were assessed by the subscales paranoid and psychoticism of the SCL-90. For both studies, the mean effect size was SMD = 0.42 (Table 4). A fixed-effect meta-analysis was performed. The pooled effect size of mood stabilizers on cognitive-perceptual symptoms (SMD = 0.42; 95% CI, −0.05 to 0.89) was not significant.

Impulsive-behavioral dyscontrol. In 6 studies,[14,34,36–38,40] impulsive-behavioral dyscontrol was assessed by the subscales anger-out and anger control of the STAXI, the subscales aggression, irritability, and suicidality of the OAS-M and OAS-M. The mean effect sizes of the individual studies varied from SMD = 0.30[34] to SMD = 3.30[40] (Table 4). As I^2 was 90%, a random-effect meta-analysis was performed. The pooled effect size of mood stabilizers on impulsive-behavioral dyscontrol (SMD = 1.51; 95% CI, 0.42–2.59) was significant ($P < .01$) and was qualified as very large.[10]

Affective dysregulation. Depressed mood. In 5 studies,[14,34–36,39] depressed mood was assessed by the HDRS, the BDI, the subscale depression of the SCL-90, and the subscale depression of the Bunney-Hamburg Rating Scale. Mean effect sizes varied from SMD = 0.45[14] to SMD = 1.07[36] (Table 4). As I^2 was 0%, a fixed effect meta-analysis was performed. The pooled effect size of mood stabilizers on depressed mood (SMD = 0.55; 95% CI, 0.21–0.90) was significant ($P < .01$) and was qualified as moderate.[10]

Anxiety. In 3 studies,[14,35,39] anxiety was assessed by the subscales obsessiveness, anxiety, and phobic anxiety of the SCL-90 and the subscale anxiety of the Bunney-Hamburg Rating Scale. The mean effect sizes of the individual studies varied from SMD = 0.44[35] to SMD = 0.95[14] (Table 4). As I^2 was 0%, a fixed-effect meta-analysis was performed. The pooled effect size of mood stabilizers on anxiety (SMD = 0.80; 95% CI, 0.38–1.21) was highly significant ($P < .001$) and was qualified as large.[10]

Anger. In 7 studies,[14,34,35,37–40] anger was assessed by the subscales state anger, anger-in, and trait anger of the STAXI, the subscales aggressiveness and anger/hostility of the SCL-90, and the subscale anger of the Bunney-Hamburg Rating Scale. Mean effect sizes varied from SMD = 0.15[34] to SMD = 3.10[39] (Table 4). As I^2 was 89%, a random-effect meta-analysis was performed. The pooled effect size of mood stabilizers on anger (SMD = 1.33; 95% CI, 0.43–2.22) was significant ($P < .01$) and was qualified as very large.[10]

Mood lability. None of the studies assessed mood lability as an outcome domain.

Global functioning. In 3 studies,[14,35,39] global functioning was assessed by the SCL-90, GAS, Global Severity Index, and Health Survey Questionnaire. Mean effect sizes varied from SMD = 0.45[35] to SMD = 0.92[14] (Table 4). As I^2 was 0%, a fixed-effect meta-analysis was performed. The pooled effect size of mood stabilizers on global functioning (SMD = 0.79; 95% CI, 0.38–1.19) was highly significant ($P < .001$) and was qualified as large.[10]

DISCUSSION

To the best of our knowledge, this is the first study applying meta-analytic techniques to quantitatively validate pharmacologic recommendations for treating specific symptom domains in severe personality disorder. The major advantage of our approach is the way we categorized the outcome variables. By disentangling the subscales of the measurement instruments used in the studies and fitting them to compatible outcome domains, we were able to conduct meta-analyses for cognitive-perceptual symptoms, impulsive-behavioral dyscontrol, affective dysregulation and its subdomains, and global functioning (Table 5). However, these outcome domains were not equally represented in the studies, and it appeared that the affective dysregulation subdomain of mood lability was unavailable for meta-analysis.

Several important findings emerged from this study. First, antipsychotics, classic as well as atypical, are effective in treating symptoms in the cognitive-perceptual domain. They have a moderate effect on schizotypal symptoms and psychotic-like features in StPD or BPD. Antipsychotics have no significant effect on impulsive-behavioral dyscontrol, but, within this class of drugs, aripiprazole seems to be effective. Within the domain of affective dysregulation, only anger is affected by antipsychotics, with a moderate to large effect. Antipsychotics have no significant effects on depressed mood and anxiety. In several (sub)domains, the atypical antipsychotic aripiprazole again seems to be a positive exception, but replication of these findings is necessary before final conclusions can be drawn. Second, antidepressants (tricyclic, MAO inhibitors, and SSRIs) do not exert effects on cognitive-perceptual symptoms or impulsive-behavioral dyscontrol and global functioning. They also lack effectiveness on depressed mood in the absence of an

Table 5. Meta-Analyses of Placebo-Controlled Randomized Clinical Trials of Pharmacotherapy in Severe Personality Disorder: Overview of Results

	Antipsychotics				Antidepressants				Mood Stabilizers			
Outcome Domain	No. of Studies[a]	Patients, n[b]	Effect Size[c]	95% CI	No. of Studies[a]	Patients, n[b]	Effect Size[c]	95% CI	No. of Studies[a]	Patients, n[b]	Effect Size[c]	95% CI
Cognitive-perceptual symptoms	5	224	0.56*	0.05 to 1.07	3	139	0.11	–0.22 to 0.45	2	74	0.42	–0.05 to 0.89
Impulsive-behavioral dyscontrol	5	261	0.26	–0.21 to 0.74	5	205	0.10	–0.17 to 0.37	6	172	1.51**	0.42 to 2.59
Affective dysregulation												
Depressed mood	5	249	0.46	–0.21 to 1.14	6	205	0.29	–0.15 to 0.72	5	148	0.55**	0.21 to 0.90
Anxiety	4	226	0.23	–0.26 to 0.72	5	193	0.30*	0.02 to 0.59	3	102	0.80***	0.38 to 1.21
Anger	4	201	0.69*	0.16 to 1.22	4	171	0.34*	0.03 to 0.65	7	230	1.33**	0.43 to 2.22
Mood lability	1	40	…	…	1	38	…	…	0	0	…	…
Global functioning	5	249	0.37**	0.12 to 0.62	4	153	0.22	–0.12 to 0.55	3	102	0.79***	0.38 to 1.19

[a]Number of studies included in meta-analysis.
[b]Sum of patients in included studies.
[c]Pooled standardized mean difference.
*$P \leq .05$.
**$P \leq .01$.
***$P \leq .001$.
Symbol: … = meta-analysis did not apply.

evident comorbid affective disorder. On the other hand, they do significantly target the subdomains of anxiety as well as anger, albeit their effectiveness is limited in magnitude. The modern SSRIs do not outperform the traditional tricyclic drugs or MAO inhibitors, with the exception of a positive effect from an unusually high dose of fluoxetine (80 mg/d) reported by Markovitz.[23] Third, conversely, mood stabilizers exert significant and very large effects on impulsive-behavioral dyscontrol and anger. Additionally, they have a large effect on anxiety and a moderate effect on depressed mood. Fourth, global functioning improves with antipsychotics and mood stabilizers but not with antidepressants. Mood stabilizers are more effective than antipsychotics in this respect.

These findings should be interpreted with clinical caution and in the light of certain methodological limitations. First, the number of well-performed PC-RCTs for personality disorders is still small, and so are numbers of participants. Because of methodological incompatibilities, 11 of 32 PC-RCTs could not be included in the meta-analyses. Second, the length of the studies was limited, so no conclusions can be drawn on the long-term use of psychotropic drugs in the treatment of severe personality disorders. Third, meta-analysis was only feasible by clustering different psychotropic drugs into 3 global classes. Subgroup analysis of traditional versus atypical antipsychotics or of tricyclic antidepressants and MAO inhibitors versus SSRIs and other second-generation antidepressants would be desirable to guide the development of new treatment algorithms. As more studies become available, more refined subgroup meta-analyses will be possible. Fourth, psychotropic drugs can have serious side effects. These were not taken into account in the meta-analyses, but should be taken into account in clinical practice. Fifth, dropout rates were substantial (3%–63%; mean, 23%), and they were highest in trials studying antipsychotics. As relevant data were lacking, it was not possible to adjust for attrition. Sixth, as is common in biomedicine, effect sizes were calculated from outcome measures at the end of the study period only, thus ignoring the fact that outcome measures can differ significantly between the active drug and placebo control groups at baseline, as was the case in some studies. As the baseline SDs of some outcome variables differed substantially, it would have made sense to take these SDs into consideration. Statistical adjustments were not feasible, however, as correlations between baseline and final assessments of outcome variables were not presented. Seventh, eligible outcome instruments and subscales were clustered on the presumption that these variables have corresponding qualities within the defined domains of symptoms and maladaptive behaviors. Yet, the validity of this presumption is unknown. Some scales may cover the content of the (sub)domains better than others. Until a generally accepted battery of outcome measures for effectiveness studies becomes available, our approach

seems to be most appropriate for evaluating literature data on this topic. Finally, having classified the outcome variables in clinical homogeneous domains and subdomains, we are aware that multiple testing might induce inflation of α errors. Yet, on the presumption that the domains and subdomains were correlated, correction for multiple testing would result in statistical overcorrection. Therefore, we have refrained from correction for multiple testing. Besides, the 95% confidence intervals presented are more informative of the statistical uncertainties. These limitations notwithstanding, the findings from this meta-analysis raise questions about American Psychiatric Association's *Practice Guideline for the Treatment of Patients with Borderline Personality Disorder*.[4] In the realm of cognitive-perceptual symptoms, the guideline proposes that traditional antipsychotics are most appropriate. Our review nevertheless suggests that atypical antipsychotics do not outperform the classic neuroleptics. With respect to impulsive-behavioral dyscontrol, the prevalent use of antidepressants (SSRIs) is not validated by this meta-analysis, nor is the second step of adding a traditional antipsychotic drug. Modern mood stabilizers seem to deserve a more prominent position. Prescribing SSRIs as first and second steps in the treatment of affective dysregulation seems outdated since mood stabilizers have a more pronounced effect.

Evidence-based pharmacologic treatment guidelines for severe personality disorders are still in their infancy. Methodologically more sound effectiveness studies, with sufficient participants and proper outcome measures, are needed. There is much to say for international collaboration as a means to devise a suitable battery of outcome instruments for effectiveness studies in personality disorders. We recommend that at least the following details be outlined in RCTs: study population (demographics and diagnoses), inclusion and exclusion criteria, treatment setting (inpatient or outpatient), type of design (eg, type randomization, observation intervals), type of treatment (eg, dosages of medication during treatment, comedication), blindness of the assessments, reliability and validity of the outcome variables, attrition rate, intent-to-treat analysis, baseline values of the outcome variables, effect sizes of intervention compared to the control group(s), and association between baseline and end point measurements of the outcome variables. Peer-reviewed publication of data should include all appropriate details in order to make them compatible for use in future systematic reviews and meta-analyses.[41,42]

Drug names: alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), phenelzine (Nardil), risperidone (Risperdal and others), topiramate (Topamax), tranylcypromine (Parnate and others).

Author affiliations: Treatment Center for Personality Disorders, Symfora Group, Centers for Mental Healthcare, Amersfoort (Dr Ingenhoven); Netherlands Institute of Forensic Psychiatry and Psychology, Pieter Baan Center, Forensic Psychiatric Observation Clinic, Utrecht (Dr Rinne); Department of Psychology and Psychotherapy, Netherlands Institute for Health Sciences, Erasmus Medical Center, Rotterdam (Drs Passchier and Duivenvoorden); and Altrecht Centers for Mental Health Care, Zeist (Ms Lafay), The Netherlands.

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