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Oxytocin in Borderline Personality Disorder

In a controlled trial, intranasal oxytocin (*Attrakt*) improved several aspects of social behavior in a group of women with borderline personality disorder.

Background: Borderline personality disorder is characterized by dysfunctions in social cognition, empathy, and social approach. There is no pharmacotherapy specifically indicated for treatment of borderline personality disorder, and psychological treatments have limited efficacy. The neuropeptide oxytocin has been shown to regulate complex social cognition and behavior in both healthy individuals and clinical populations, and some evidence suggests peripheral oxytocin levels are reduced in women with the disorder.

Methods: Study subjects were 51 women with a DSM-IV diagnosis of borderline personality disorder and 51 age-matched healthy controls. Participants received randomized double-blind treatment with a single intranasal dose of 24 IU oxytocin or placebo 45 minutes before completing a standardized task measuring affective and cognitive empathy and approach motivation. Women receiving hormonal contraception were excluded as were controls with any psychiatric disorder and women with schizophrenia, bipolar disorder, or substance abuse comorbid with borderline personality disorder. Because pharmacotherapy for other comorbid conditions is common in patients with borderline personality disorder, medicated patients were not excluded. Testing was undertaken while women were in the mid-luteal phase of their menstrual cycle, and comprised presenting participants a series of pictures showing people in positive and negative emotionally-laden situations. Cognitive empathy was evaluated by asking participants to select the correct mental state description of the individual pictured. Likert scales were used to assess affective empathy (i.e., participants' level of empathic concern for the person pictured) and approach motivation (participants desire to be close to the depicted person).

Results: Participants had an average age of about 30 years. Comorbidity was common and 61% of women with borderline personality disorder were receiving pharmacotherapy for comorbid conditions including major depression, anxiety disorders, and PTSD. Compared with healthy controls, women with borderline personality disorder demonstrated significantly reduced cognitive and affective empathy ($p \leq 0.02$) and less approach behavior motivation ($p=0.002$).

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Overall, intranasal oxytocin significantly increased affective empathy and approach motivation in both patients with borderline personality disorder and in healthy controls. Cognitive empathy was not increased in either group. In the borderline personality group, compared with placebo, oxytocin significantly improved scores for affective empathy (p=0.011; effect size,* 0.68) and approach motivation (p=0.002; effect size, 0.91). On both measures, actively-treated women with borderline personality disorder improved to a level comparable to that in healthy controls who received placebo. Effects of oxytocin in the clinical group were not altered by baseline symptom severity, and effects of oxytocin on mood, anxiety, anger, and distress were not correlated with improvements in social behavior.

Discussion: These results provide initial evidence of a beneficial effect of a single dose of oxytocin on affective empathy and approach motivation in women with borderline personality disorder. Additional study is needed to determine if the effects will carry over to male patients and to evaluate the long-term effects.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Domes G, Ower N, von Dawans B, Spengler F, et al: Effects of intranasal oxytocin administration on empathy and approach motivation in women with borderline personality disorder: a randomized controlled trial. *Translational Psychiatry* 2019; doi 10.1038/s41398-019-0658-4. From the University of Freiburg; and the University of Trier, Germany. **Funded by the German Research Foundation; and other sources. The authors declare no competing interests.**

***See Reference Guide.**

Antidepressant Withdrawal Syndromes

Withdrawal phenomena with antidepressants may be a far more important and complex problem than current treatment guidelines imply. According to a review, guidelines such as those of the American Psychiatric Association may minimize the frequency and seriousness of these reactions.

The APA guideline uses the term "discontinuation syndrome" in reference to antidepressants, rather than the "withdrawal syndrome" used with other psychotropic drugs. This may imply that antidepressant withdrawal is free of clinical implications and can be prevented by gradually withdrawing the drug. Symptoms of antidepressant withdrawal syndrome typically appear within 3 days of stopping an antidepressant or initiating a taper. Untreated symptoms may be mild and resolve spontaneously over several weeks, or they may persist for months or longer. A persistent postwithdrawal disorder has been described wherein the original illness returns with a greater intensity than prior to treatment and with additional clinical features or symptoms that had not previously occurred. New-onset symptoms may occur after abruptly stopping antidepressants in up to 40% of patients and may be equally likely with gradual tapering, according to a systematic review.

The pharmacokinetic model of withdrawal syndromes supports the gradual withdrawal of antidepressants or the switch from short elimination half-life agents to fluoxetine (*Prozac*). However, this model does not account for all of the discontinuation-related phenomena, including persistent postwithdrawal disorder and behavioral toxicity, which can manifest as switching to hypomania and a bipolar course, loss of treatment effect, refractoriness to previously effective treatment, and paradoxical worsening of depression.

The pharmacodynamic model, or oppositional model of tolerance, was first described more than a decade ago and is being supported increasingly by clinical studies. This model proposes that continued drug treatment recruits processes that oppose the initial acute effects of the drug and may eventually move the illness to a more malignant and treatment-unresponsive course. During treatment, these oppositional processes may result in delayed adverse effects such as

weight gain, loss of efficacy, and mania or hypomania. After discontinuation, the oppositional process may continue for a few weeks or months or for years. The oppositional processes are influenced by genetics, but more strongly by factors such as the duration and type of treatment and the history of prior antidepressant use, augmentation, and switching.

Management of withdrawal syndromes requires the clinician first to differentiate among the symptoms of depression relapse and recurrence, new withdrawal symptoms, rebound of the original symptoms at an increased intensity, and persistent postwithdrawal disorder. Optimal tapering strategies to avoid these problems have not been researched, and not all patients can be switched to fluoxetine, which is less likely to cause withdrawal. If withdrawal syndromes occur, reintroducing the initial antidepressant or switching to fluoxetine may not ameliorate the symptoms, as tolerance does not necessarily develop to a single drug, but to a particular effect, which may be shared by other medications of the same class. Alternate strategies, which await research, include switching to a different class of medication and various psychotherapies. Discontinuing antidepressants may also have unanticipated effects on concomitant medications for medical illnesses and they should be withdrawn only with medical and psychotherapeutic support.

Fava G, Cosci F: Understanding and managing withdrawal syndromes after discontinuation of antidepressant drugs. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.19com12794. From the State University of New York, Buffalo; and the University of Florence, Florence, Italy. **This literature review was not funded. The authors declared no relevant financial relationships.**

Antidepressants and Adverse Health Outcomes

A synthesis of evidence from previously published meta-analyses found no conclusive evidence supporting an association between antidepressant use and commonly reported adverse health outcomes. The few associations that were initially supported were likely due to confounding by indication.

Background: While randomized clinical trials provide strong evidence for the efficacy and acceptability of antidepressants, safety assessment is inherently biased by methodological weaknesses including small and unrepresentative samples, and short exposure durations in the studies. In contrast, observational studies provide real-world data and may provide a more accurate safety picture. The present umbrella review* was undertaken to synthesize the evidence from observational studies regarding potential adverse outcomes with antidepressant treatment.

Methods: Peer-reviewed meta-analyses of observational cohort, case–control, or nested case-control studies examining antidepressant use and any adverse health outcome were identified by systematic literature search. Significant associations found in the individual meta-analyses were categorized according to the strength of the findings (i.e., sample size, strength of the association, and assessment of the presence of biases) and stratified into mutually exclusive credibility categories: convincing; highly suggestive; suggestive; or weak. (See table, next page.)

Results: A total of 45 meta-analyses were included in the umbrella review: 695 studies assessing 13 presumed antidepressant risks found >100 significant associations. The most commonly examined associations, in 62% of the studies, concerned pregnancy-related or maternal complications, and most associations (67%) related to SSRIs or SNRIs. Convincing evidence supported only 3 of the 102 significant associations: SSRI use and increased risk of suicide attempt or completion in children and adolescents; antidepressant exposure before pregnancy and autism in the offspring; and SSRI use during pregnancy and autism in the offspring. Several other adverse health outcomes including bleeding, fracture, cataracts, maternal complications of pregnancy, poor neonatal outcomes, and ADHD in exposed

offspring, all of which had been found to be significantly associated with antidepressant use, were supported by highly suggestive evidence. None of the associations were proven to be causal and none remained convincing after accounting for confounding by indication.

Criteria for Credibility of Evidence Categories	
Convincing Evidence	>1000 Cases Significant summary associations per random-effects calculations No evidence of small-study effects No evidence of excess of significance bias Prediction intervals not including the null value Largest study at least nominally significant ($p < 0.05$) No large heterogeneity
Highly Suggestive Evidence	>1000 Cases Significant summary associations per random-effects calculation Largest study at least nominally significant ($p < 0.05$)
Suggestive Evidence	>1000 Cases Significant summary associations per random-effects calculations
Weak Evidence	All other associations with at least nominal significance ($p<0.05$)

Discussion: Overall, these results suggest that the previously reported associations between antidepressant use and adverse health outcomes are not supported by convincing evidence. Antidepressant use appears to be safe, and no absolute contraindications to antidepressant use were found. However, additional study is warranted to clarify the degree of confounding by indication.

Dragioti E, Solmi M, Favaro A, Fusar-Poli P, et al: Association of antidepressant use with adverse health outcomes: a systematic umbrella review. *JAMA Psychiatry* 2019; doi :10.1001/jamapsychiatry.2019.2859. From Linkoping University, Sweden; and other institutions. **Funded by South London and Maudsley NHS Foundation Trust; and King's College London, U.K. Four of 17 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Sublingual Atropine for Sialorrhea

A review of published cases suggests that sublingual use of atropine ophthalmic drops (*Isopto Atropine*) may be an effective treatment for clozapine-associated sialorrhea.

Sialorrhea may affect more than 30% of clozapine-treated patients and can cause dermatological complications, negatively affect sleep, and increase risk for aspiration pneumonia. In addition, psychosocial effects could lead to clozapine noncompliance. Treatment options include anticholinergics and α2-agonists, but adverse effects and limited effectiveness are common. Atropine has been suggested as an additional option based on its activity as a competitive antagonist of acetylcholine on the muscarinic receptors in the salivary glands.

A literature search identified 6 articles describing the use of sublingual atropine in the treatment of clozapine-induced sialorrhea (2 individual case reports and 4 case series; 14 total patients). An additional 6 studies were identified of its use for sialorrhea of another etiology (1 randomized clinical trial, 2 pilot studies, 1 open-label study, and 2 case reports; 67 patients).

Of those treated for clozapine-associated sialorrhea, 8 patients (57%) experienced complete resolution and 3 patients (21%) substantial improvement with 1–2 drops of sublingual atropine 1% ophthalmic drops. Three patients experienced an adverse event: xerostomia in 1 patient; another patient with disorganized schizophrenia used the entire bottle; and the third patient administered the drops in his eye resulting in temporarily impaired vision. Studies in patients with other etiologies (e.g., cerebral palsy, Parkinson's disease, autism, GI cancer) also showed positive effects of atropine on sialorrhea. Xerostomia was the only adverse effect determined to be related to treatment.

While the evidence base for sublingual atropine treatment of clozapine-induced sialorrhea is very limited, the positive effects taken with the demonstrated efficacy in patients with other causes suggest it may be an option that is safe and effective. However, large-scale controlled trials using standardized assessments and methodical evaluation of systemic absorption of atropine are needed.

Van der Poorten T, De Hert M: The sublingual use of atropine in the treatment of clozapine-induced sialorrhea: a systematic review. *Clinical Case Reports* 2019;7:2108–2113; doi 10.1002/ccr3.2431. From Katholieke Universiteit Leuven; and the University of Antwerp, Belgium. **Source of funding not stated. The authors declared no competing interests.**

Antipsychotic Metabolic Effects

According to a meta-analysis, metabolic adverse effects vary widely across antipsychotic medications. Clozapine and olanzapine appear to have the highest metabolic burden, while aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone appear to be associated with better metabolic outcomes.

Methods: A comprehensive literature search identified all randomized double-blind trials of antipsychotic treatments in adults experiencing an acute exacerbation of schizophrenia or a related disorder. Network meta-analyses* evaluated whether body weight, age, sex, ethnicity, or treatment factors, were related to changes in metabolic parameters. Additionally, potential associations between changes in weight, body mass index (BMI), and metabolic parameters and change in total symptoms scores on the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS) were assessed.

Results: A total of 100 studies with nearly 26,000 patients met inclusion criteria. Antipsychotic treatments included amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, flupenthixol, fluphenazine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine. The mean patient age in the total sample was 35 years, and 58% of participants were men. Study durations ranged from 2 to 13 weeks.

For change in weight (83 studies; 18 individual antipsychotics) brexpiprazole, risperidone and paliperidone, quetiapine, iloperidone, sertindole, olanzapine, zotepine, and clozapine were associated with significant weight gain. BMI increases (22 studies; 9 individual antipsychotics) were found with lurasidone, risperidone and paliperidone, quetiapine, sertindole, clozapine, and olanzapine. Total cholesterol (36 studies; 14 antipsychotics) was increased with quetiapine, olanzapine, and clozapine. LDL cholesterol (24 studies; 9 antipsychotics) was decreased with cariprazine and increased with quetiapine and olanzapine. HDL cholesterol (22 studies; 10 antipsychotics) increased with aripiprazole and brexpiprazole. Triglyceride concentrations (34 studies; 15 antipsychotics) increased with quetiapine, olanzapine, zotepine, and clozapine. Fasting-glucose levels (37 studies; 16 antipsychotics) were reduced with lurasidone and increased with olanzapine, zotepine, and clozapine.

Agents that were associated with each individual metabolic parameter were ranked using P-scores on a continuous scale from 0 to 1. Higher scores indicate a greater increase in the metabolic parameter, with the exception of HDL cholesterol, for which a higher P-score indicates a smaller increase. (See table, next page.) For weight gain, haloperidol was ranked best and clozapine worst. For BMI increase haloperidol was ranked best and olanzapine worst. For total cholesterol alteration cariprazine was ranked best and clozapine worst. For change in LDL cholesterol cariprazine was ranked best and olanzapine worst. For HDL cholesterol alteration brexpiprazole was ranked best and amisulpride worst. For triglycerides brexpiprazole ranked as best and clozapine worst. For total glucose levels lurasidone was ranked best and clozapine worst.

Antipsychotic drugs ranked according to associated degree of alteration in bodyweight, body-mass index, and metabolic parameters							
	Weight	**BMI**	**Glucose**	**LDL Cholesterol**	**HDL Cholesterol**	**Total Cholesterol**	**Triglycerides**
Haloperidol	0.10	0.08	0.59	—	—	0.59	0.63
Ziprasidone	0.10	—	0.42	0.12	0.24	0.25	0.33
Aripiprazole	0.26	0.11	0.55	0.48	0.26	0.50	0.33
Lurasidone	0.32	0.37	0.09	0.27	0.45	0.27	0.26
Cariprazine	0.37	—	0.70	0.07	0.47	0.16	0.28
Fluphenazine	0.38	—	—	—	—	—	—
Amisulpride	0.41	—	0.14	—	0.83	0.64	0.42
Brexipiprazole	0.45	—	0.40	0.66	0.18	0.52	0.23
Flupenthixol	0.44	—	—	—	—	—	—
Asenapine	0.56	—	0.22	—	—	—	—
Risperidone, Paliperidone	0.58	0.56	0.46	0.54	0.51	0.55	0.39
Quetiapine	0.65	0.68	0.47	0.91	0.59	0.82	0.71
Iloperidone	0.70	—	0.73	—	—	0.19	0.63
Sertindole	0.81	0.72	0.36	—	—	0.26	0.29
Zotepine	0.88	—	0.94	—	—		0.94
Clozapine	0.90	0.85	0.97	—	—	0.97	0.97
Olanzapine	0.92	0.93	0.67	0.96	0.76	0.91	0.83
—Indicates comparisons that are not available							

Greater antipsychotic-induced increases in total cholesterol were associated with a larger proportion of non-white participants. There was no strong evidence of an association between change in weight, BMI, LDL cholesterol, HDL cholesterol, or triglycerides with any baseline variables. Greater symptom improvement was strongly associated with larger increases in body weight, BMI, total cholesterol, and LDL cholesterol, and with greater reductions in HDL cholesterol. No association was found between symptom change and changes in triglyceride or glucose levels.

Discussion: As expected, clozapine and olanzapine were associated with the greatest degree of metabolic dysregulation across nearly all parameters. Higher baseline bodyweight, male sex, and nonwhite ethnicity predicted greater vulnerability to antipsychotic-induced metabolic dysregulation. The finding that symptom improvements were associated with increases in weight, BMI, total cholesterol and LDL cholesterol concentrations, and decreases in HDL cholesterol concentrations may suggest that the most effective agents are associated with the greatest metabolic disturbance. Alternatively, the findings may reflect medication compliance, with poor compliance resulting in reduced efficacy and fewer metabolic effects.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Pillinger T, McCutcheon R, Vano L, Mizuno Y, et al: Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry* 2019; doi 10.1016/S2215-0366(19)30416-X. From King's College, London, U.K.; and other institutions. **Funded by the U.K. Medical Research Council; and other sources. Two of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: **amisulpride (not available in the U.S.)—*Solian*; aripiprazole—*Abilify*; asenapine—*Saphris*; brexpiprazole—*Rexulti*; cariprazine—*Vraylar*; clozapine—*Clozaril*; flupenthixol (not available in the U.S.)—*Depixol*; fluphenazine—*Prolixin*; haloperidol—*Haldol*; iloperidone—*Fanapt*; lurasidone—*Latuda*; olanzapine—*Zyprexa*; paliperidone—*Invega*; quetiapine—*Seroquel*; risperidone—*Risperdal*; sertindole (not available in the U.S.)—*Serdolect*; ziprasidone—*Geodon*; zotepine (not available in the U.S.)—*Zoleptil***

***See Reference Guide.**

Duloxetine-Induced Acute Liver Injury

A 37-year-old woman with a history of major depressive disorder, unspecified anxiety disorder, alcohol use disorder, and opioid use disorder was admitted for acute stabilization after reporting suicidal ideation. On admission, liver function tests were unremarkable and she was receiving no medication. Treatment was initiated with 40 mg/day duloxetine, and she reported a rapid improvement in depressive symptoms. On day 4, duloxetine was increased to 60 mg/day to address residual symptoms. Within 24 hours the patient demonstrated significant anxiety, bilateral tremors, hyperthermia, diaphoresis, autonomic instability, and mild upper right quadrant tenderness. Repeat liver function tests showed significant increases in alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT; see table). Duloxetine was discontinued and over the subsequent week symptoms resolved and liver enzymes normalized.

Liver Enzyme Values

Time	ALP (U/L)	AST (U/L)	ALT (U/L)
Reference Range	38–126	17–59	11–58
Baseline	57	20	12
1 day after dosage increase	105	203	156
2 days after discontinuation	101	49	93
7 days after discontinuation	83	25	37

There have been previous reports of liver enzyme elevations and rare reports of liver damage with duloxetine. Although this patient had risk factors for hepatic dysfunction

(e.g., female sex, alcohol consumption), no underlying disease process (e.g., viral hepatitis) was identified and baseline function was normal. This report highlights the possibility for acute, dose-dependent, liver injury to occur with rapid duloxetine titration.

Kassam A, Cunningham E, Musco S: Dangers of rapid dosing: a case of dose-dependent drug-induced liver injury from duloxetine. *Journal of Clinical Psychiatry* 2019; doi:10.4088/PCC.18I02333. From Community Health Network; and other Butler University, Indianapolis, IN. **This report was unfunded. The authors declared no competing interests.**

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Network Meta-Analysis: A meta-analytic technique that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method allows simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these two trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the two options have never been directly compared.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

Umbrella Review: A study design that allows the findings of reviews to be compared and contrasted. The most characteristic feature is that this type of evidence synthesis only considers the highest level of evidence, namely other systematic reviews and meta-analyses, for inclusion.

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