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Blue again: Perturbational effects of antidepressants suggest monoaminergic homeostasis in major depression

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Abstract (253 words)

Some evolutionary researchers have argued that current diagnostic criteria for major depressive disorder (MDD) may not accurately distinguish true instances of disorder from a normal, adaptive stress response. According to disorder advocates, neurochemicals like the monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) are dysregulated in major depression. Monoamines are normally under homeostatic control, so the monoamine disorder hypothesis implies a breakdown in homeostatic mechanisms. In contrast, adaptationist hypotheses propose that homeostatic mechanisms are properly functioning in most patients meeting current criteria for MDD. If the homeostatic mechanisms regulating monoamines are functioning properly in these patients, then oppositional tolerance should develop with prolonged antidepressant medication (ADM) therapy. Oppositional tolerance refers to the forces that develop when a homeostatic mechanism has been subject to prolonged pharmacological perturbation that attempt to bring the system back to equilibrium. When pharmacological intervention is discontinued, the oppositional forces cause monoamine levels to overshoot their equilibrium levels. Since depressive symptoms are under monoaminergic control, this overshoot should cause a resurgence of depressive symptoms that is proportional to the perturbational effect of the ADM. We test this prediction by conducting a meta-analysis of ADM discontinuation studies. We find that the risk of relapse after ADM discontinuation is positively associated with the degree to which ADMs enhance serotonin and norepinephrine in prefrontal cortex, after controlling for covariates. The results are consistent with oppositional tolerance, and provide no evidence of malfunction in the monoaminergic regulatory mechanisms in patients meeting current diagnostic criteria for MDD. We discuss the evolutionary and clinical implications of our findings.

Introduction

Depression is an affective state of negative mood and low arousal. According to the current text revision version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), a bout of depression constitutes an episode of major depressive disorder (MDD) if it is denoted by at least five of nine symptoms: (1) depressed mood; (2) anhedonia; (3) significant weight loss (or gain), or a decrease (or increase) in appetite; (4) insomnia (or hypersomnia); (5) psychomotor retardation (or agitation); (6) fatigue or loss of energy; (7) feelings of worthlessness or guilt; (8) diminished ability to concentrate; and (9) recurrent thoughts of death (not just fear of dying), or suicidal thoughts or actions. One of the symptoms must be either depressed mood or anhedonia. Additionally, the episode must last for at least two weeks, and it must cause substantial distress or impairment in an important domain of functioning. Finally, the episode must not be better accounted for by bereavement (which assumes that the episode is not disordered if it causes significant impairment for up to two months), and must not be caused by a substance or a medical condition (American Psychiatric Association, 2000).

Millions of people are affected by depression each year. Approximately 6.6% of adults, or about 13 million of the adult US population, are estimated to have had episodes that meet current criteria for MDD within a year's time (Kessler, Merikangas, & Wang, 2007). Based on a single interview, the lifetime prevalence of MDD is estimated to be 16.2%, or 33 million of the adult population (Kessler et al., 2007). However, lifetime estimates from single interviews are conservative because interviewees vary greatly in their current age and they have difficulty recalling prior episodes of depressive symptoms (Kessler, Berglund, Demler, Jin, & Walters, 2005; Kruijshaar et al., 2005; Moffitt et al., 2009; Wells & Horwood, 2004). Longitudinal studies of community samples in which participants are repeatedly interviewed yield higher estimates of the lifetime prevalence of MDD, often exceeding 40% (Kruijshaar et al., 2005; Moffitt et al., 2009; Wells et al., 2004).

Most episodes that meet diagnostic criteria for MDD are associated with stressors (e.g., bereavement, marital difficulties, interpersonal conflict, financial difficulties, health issues). For instance, in a longitudinal study of a large community sample of twins of both sexes, 88.1% of diagnosed episodes of MDD were associated with a stressor of some sort (Keller, Neale, & Kendler, 2007). Only 11.9% of episodes appeared to be endogenous (depression in the absence of an environmental trigger). However, even many of the apparently endogenous episodes could have reflected a reluctance to disclose stressors of a sensitive nature (Leff, Roatch, & Bunney, 1970).

There are two broadly divergent approaches to the relationship between stressors and depression. In some way, the relationship must be mediated by the brain, but the neurological causes of depression are generally acknowledged to be unknown (Berton & Nestler, 2006). Many researchers, certain that depressive symptoms are maladaptive, search for evidence of stress-induced malfunction in the brain (for recent reviews, see (Krishnan & Nestler, 2008; Savitz & Drevets, 2009)). These researchers attempt to identify the neurological mechanisms responsible for the chronic nature of depression and its association with a variety of medical conditions (McEwen, 1998; McEwen, 2007), the structural changes in the brain associated with

depression and their effects on cognition (Duman, 2004; Duman & Monteggia, 2006; Sapolsky, 1996; Sapolsky, 2000; Sapolsky, 2001; Savitz et al., 2009), and the neurochemical pathways of depression, including the mechanisms by which antidepressant medications (ADMs) reduce symptoms (for a review, see (Krishnan et al., 2008)). An integrating theme in this research is that the neurochemistry of depression is disordered, although the precise neurochemicals that are dysregulated are the subject of much debate and research. Monoamine neurotransmitters, glucocorticoids, neurotrophins, and cytokines are the major chemicals thought to be involved in depression (Krishnan et al., 2008). Regardless of the role of other chemicals, there seems to be consensus that the monoamine neurotransmitters—particularly serotonin (5-hydroxytryptamine or 5-HT), norepinephrine (NE), and, to a lesser extent, dopamine (DA)—are directly or indirectly involved in the biochemical pathways to depression (Krishnan et al., 2008). All ADMs, for instance, act on monoamines through a variety of mechanisms (see below). Moreover, research on rodents in which monoaminergic receptors have been knocked out, or monoamine transmission has been disabled, has provided strong experimental evidence that monoamines play a role in depressive symptoms and in the antidepressant response, particularly 5-HT and NE (Cryan et al., 2004; Dziedzicka-Wasylewska et al., 2006; Heisler et al., 1998; Mayorga et al., 2001).

Other researchers argue that depressive symptoms might be better described by adaptive mechanisms that respond to stressors and threats (Allen & Badcock, 2003; Allen & Badcock, 2006; Andrews & Thomson, Jr., 2009; Gilbert, 2006; Hagen, 2003; Horwitz & Wakefield, 2007; Nesse, 2000; Nesse, 2004; Nesse & Ellsworth, 2009; Price, Sloman, Gardner, Gilbert, & Rohde, 1994; Price, 2009; Watson & Andrews, 2002). These hypotheses do not propose that all episodes of depression are adaptive since all evolved adaptations in the body are susceptible to malfunction and disorder at some rate. Rather, the issue is whether the symptoms currently used to diagnose depressive disorder accurately distinguish the disordered state from normal, adaptive processes (Horwitz et al., 2007; Spitzer & Wakefield, 1999; Wakefield, Schmitz, First, & Horwitz, 2007; Wakefield, Schmitz, & Baer, 2010). Some adaptationist hypotheses restrict their application to symptoms and episodes that do not meet diagnostic thresholds, but such restrictions are intended to exclude true instances of disorder. Consequently, these hypotheses are not falsified in any rigorous sense by evidence that current diagnostic criteria are inaccurate. In any event, evolutionarily oriented researchers tend to focus on the ecological mapping of the symptoms of depression (and the cognitive and behavioral outputs) to the stressors that trigger episodes (Andrews et al., 2007; Badcock & Allen, 2003; Gilbert & Allan, 1998; Gilbert, Gilbert, & Irons, 2004; Hagen, 1999; Hagen, 2002; Keller & Nesse, 2004; Keller & Nesse, 2005; Keller & Nesse, 2006; Wrosch & Miller, 2009), largely treating the brain as a black box whose internal structure and operation are unknown.

Both approaches agree that the body has evolved adaptations for responding to stress. They both believe that, in general, environmental stressors trigger mechanisms in the body that regulate multiple body systems so that cognition and behavior can be adaptively modulated to meet the environmental challenge. They also agree that these evolved stress response mechanisms can malfunction. They primarily differ in what constitutes evidence of depressive disorder and the causes of depressive disorder.

Most articulations of the monoamine disorder hypothesis propose that forebrain levels of monoamine neurotransmitters are depleted in depressive disorder—particularly serotonin (5-HT), norepinephrine (NE) and, to a lesser extent, dopamine (DA). However, some have suggested that monoaminergic transmission may be enhanced in depression (Sapolsky, 2004). The precise direction of association between depression and forebrain monoamine levels is not crucial for the present paper. It is sufficient to say that the neurochemical disorder hypothesis proposes that monoamines, particularly 5-HT and NA, are perturbed in some way.

But monoaminergic perturbation, per se, is not evidence of disorder. The most prominent definition of disorder is based in evolutionary theory (Spitzer, 2007), and it argues that at heart of every disorder is an evolved adaptation that is malfunctioning (Wakefield, 1992). Under this definition, the claim that depression is a disorder of too much or too little of a neurotransmitter is ultimately a claim that the evolved mechanisms that control neurotransmitter levels are malfunctioning.

Monoamine neurotransmitter levels are normally under homeostatic control (Best, Nijhout, & Reed, 2010). *Homeostasis* involves the regulation of an important substance or physiological parameter within a narrow range around an equilibrium. Minimally, homeostatic mechanisms have a sensor for determining how far the parameter deviates from the equilibrium and feedback mechanisms for bringing the parameter back to equilibrium (Woods, 2009). For instance, the homeostatic control of core body temperature involves neuronal sensors in the preoptic anterior hypothalamus that connect with various efferent pathways to exert feedback and keep temperature at equilibrium (Romanovsky, 2007). Additionally, many homeostatic mechanisms can raise or lower the equilibrium in response to environmental contingencies. Thus, the body often responds to an infection by raising the core body temperature equilibrium—otherwise known as fever (Romanovsky et al., 2005). Feedback mechanisms then maintain core body temperature around this elevated equilibrium. Because some infections last for weeks or months, fever can last for extended periods of time.

If depression is, in whole or in part, a disorder in the homeostatic mechanisms that regulate monoamine transmission, then it could involve malfunction in: (1) the sensors that monitor monoamine levels (2) the feedback mechanisms that maintain monoamine levels at the equilibrium; or (3) the mechanisms that alter the equilibrium point.

Although most adaptationist research treats the brain as a black box, a common (if unstated) implication of all adaptationist hypotheses for depression is that the relevant neurochemistry is altered to change cognitive and behavior in ways that adapt the organism to the environmental contingencies that triggered the episode. An adaptationist perspective on the chronic nature of depression suggests that, like fever, monoamines may be under the control of a homeostatic mechanism that maintains forebrain levels at an altered equilibrium for an extended period of time, presumably because the nature of the stressor requires it (see, e.g., Andrews et al., 2009).

The disruption of a mechanism by pharmacological intervention can reveal whether it is under homeostatic control (Young & Goudie, 1995). Acute exposure to opiates inhibits the firing of noradrenergic neurons in the locus coeruleus by suppressing cyclic adenosine 3',5'-

monophosphate (cAMP) levels (Nestler & Aghajanian, 1997). However, with long-term (chronic) exposure, firing rates return to normal because a negative feedback mechanism upregulates the cAMP pathway so that it counteracts the drug's effect and returns the system to the equilibrium (Nestler et al., 1997). The neurological changes brought about by homeostatic mechanisms that counteract the disrupting effects of chronic drug exposure are referred to as *oppositional tolerance* (Fava & Offidani, 2011; Young et al., 1995). These counteractive forces can cause the system to overshoot the equilibrium when the drug is abruptly discontinued (Fava et al., 2011; Young et al., 1995). Thus, when an opioid receptor antagonist is used to abruptly block an opiate, the upregulated cAMP pathway causes firing rates to exceed the normal rate (Nestler et al., 1997).

Some researchers have called for greater research on the neurological responses of homeostatic mechanisms to chronic psychotropic drug use, including ADMs (Hyman & Nestler, 1996). Others have specifically hypothesized that oppositional tolerance to ADMs may develop in depression (Fava et al., 2011). Whether the monoamines thought to cause major depression are under homeostatic control has important implications for debates about whether most episodes of MDD are instances of a properly functioning adaptation or true instances of disorder. Homeostatic mechanisms are classic examples of adaptations. Survival and reproduction require the internal environment of the organism to be regulated (Hochochka & Somero, 2002; Woods, 2009). The machinery needed to exert negative feedback to maintain physiological conditions within a narrow band around an equilibrium are often complex and difficult to explain by any process other than natural selection. Consequently, evidence that monoamine neurotransmitters were under homeostatic control in patients diagnosed with MDD would suggest that those mechanisms were not malfunctioning.

In this paper, we focus on a straightforward implication of the hypothesis that depression neurochemistry is under homeostatic control: ADM-induced perturbations to monoamine neurotransmitter levels should trigger oppositional tolerance. Previous research provides some support for oppositional tolerance to ADMs in patients diagnosed with MDD. It is not uncommon for depressive symptoms to reemerge after remission while patients are on maintenance ADM therapy (Byrne & Rothschild, 1998), which is consistent with tolerance (Fava et al., 2011). Other support comes from a meta-analysis of studies examining the risk of relapse among patients with remitted symptoms after ADM treatment had been discontinued (Viguera, Baldessarini, & Friedberg, 1998). The authors found that the risk of relapse was positively associated with the duration of ADM treatment. While this relationship was not statistically significant, it became marginally significant in a reanalysis that included an additional study (Baldessarini, Ghaemi, & Viguera, 2002). Such evidence suggests oppositional tolerance because longer treatment periods provide homeostatic mechanisms with more time to make neurological changes that oppose pharmacological perturbation (Fava et al., 2011). However, several subsequent meta-analyses have failed to find any evidence that treatment duration affected the risk of relapse after discontinuation (Geddes et al., 2003; Glue, Donovan, Kolluri, & Emir, 2010; Kaymaz, van Os, Loonen, & Nolen, 2008). At present, evidence of oppositional tolerance in depression is equivocal.

ADMs vary widely in the degree to which they perturb monoamine levels in the brain (see below). Consequently, perturbational differences in ADMs could affect the degree of

oppositional tolerance. This is analogous to the negative feedback forces that springs exert when they are displaced from their equilibrium position. As one pulls a spring from its equilibrium position, the spring exerts an oppositional force that attempts to bring the spring back to equilibrium; the more further one displaces the spring from its equilibrium position, the greater the oppositional force that the spring produces. Similarly, ADMs with greater perturbational effects should trigger stronger oppositional forces that attempt to bring monoamine levels back to equilibrium. The buildup of oppositional tolerance under ADM treatment could then cause the system to overshoot its equilibrium upon discontinuation, and the degree of overshoot should be proportional to the perturbational effect of the ADM.

We hypothesize that monoamine levels are under homeostatic control in patients diagnosed with MDD, and that ADM treatment will cause oppositional tolerance. There are two implications for the present paper. First, the buildup of oppositional tolerance during ADM treatment will attempt to bring monoamine levels back to equilibrium, which will cause them to overshoot the equilibrium after ADM treatment is discontinued. Second, the degree to which monoamine levels overshoot the equilibrium will be positively related to the perturbational effect of the ADM. We do not directly test these implications because we lack relevant perturbational data in humans. Rather, we test two predictions that follow from them.

Since depressive symptoms are under monoaminergic control, ADM treatment tends to decrease depressive symptoms. However, oppositional tolerance during ADM treatment should build pressure for increasing symptoms (Fava et al., 2011). After ADM treatment is discontinued, the overshoot of monoamines will cause an increase in symptoms that could exceed diagnostic thresholds for a relapse or a recurrence of MDD (hereafter, just *relapse*). Since oppositional tolerance will be absent in patients who resolve their episodes without ADM treatment, we predict that the risk of relapse among patients who discontinue ADM treatment will be higher than the risk of relapse among patients who remit without ADM treatment. Second, and more importantly, we predict that the risk of relapse will be positively related to the perturbational effect of the ADM.

We conduct a meta-analysis to test these predictions. Other meta-analyses of ADM discontinuation studies have been conducted (Geddes et al., 2003; Glue et al., 2010; Kaymaz et al., 2008; Viguera et al., 1998), but they have not been specifically designed to address these questions. Moreover, our meta-analysis offers an important methodological improvement. ADM discontinuation studies vary widely in the criteria that are used to define a relapse. Some studies use a threshold score on a single assessment instrument, while others may use a complex combination of different instruments assessed over multiple time periods. These definitional criteria can have a dramatic affect on the relapse rate (Keller et al., 1998; Montgomery & Dunbar, 1993a). Studies that use more stringent relapse criteria make it more difficult for an increase in symptoms to qualify as a relapse, resulting in lower relapse rates (Montgomery et al., 1993a). Prior meta-analyses have not attempted to control for the variability in the stringency of relapse criteria in discontinuation studies, possibly because it is difficult to objectively compare relapses defined by different instruments. For each study, we construct a variable (called *stringency*) that can be objectively calculated as the number of assessment hurdles that have to be passed before an increase in symptoms will be defined as a relapse. In general, studies with

more assessment hurdles should make it more difficult for an increase in symptoms to qualify as a relapse. If so, our stringency variable should be a negative predictor of the relapse rate.

Before describing the design of our meta-analysis in detail, we discuss how the major ADM classes differ in the degree to which they perturb monoamine neurotransmitter levels.

Perturbational effects of ADMs

Monoaminergic neurons originate in various areas of the midbrain and project to forebrain regions. After monoamines are released into the synapse, they are eventually taken back into the presynaptic neuron by molecules called transporters. Once they are taken back inside the cell, monoamines are broken down by two enzymes—monoamine oxidase A (MAO-A), which breaks down 5-HT, NE, and DA, and monoamine oxidase B (MAO-B), which breaks down DA, but not 5-HT or NE.

All ADMs have multiple pharmacological effects by binding to various receptors, transporters, and enzymes. This could make it difficult to classify them in terms of their perturbational impact. However, one relatively clear measure of perturbational impact is by whether cortical levels of the monoamine neurotransmitters—5-HT, NE, and DA—are actually affected. When cortical levels of a neurotransmitter are influenced by an ADM, the drug exerts perturbational influence through all the receptors, transporters, and enzymes to which the neurotransmitter binds.

The perturbational effects of ADMs on monoamine forebrain levels have not been directly measured in humans because it requires invasive techniques. However, microdialysis studies of rodents have examined the perturbational effects of ADMs in various brain regions. Since there is regional variability in the effects of ADMs, we look at microdialysis studies assessing the *in vivo* effects of ADMs on rodent medial prefrontal cortex (mPFC) monoamine levels. We choose the mPFC because it plays an important role in behavioral depression in rodents (Amat et al., 2005; Amat, Paul, Zarza, Watkins, & Maier, 2006; Amat, Aleksejev, Paul, Watkins, & Maier, 2010; Baratta et al., 2009). In human depression, the ventrolateral prefrontal cortex (VLPFC) is thought to be important (Andrews et al., 2009; Drevets, 1998), which may seem incongruent with the rodent literature. However, the rodent brain is organized differently than the human brain, and the rodent mPFC is a likely structural and functional homologue to the human VLPFC (Kesner, 2000; Uylings & Vaneden, 1990; Uylings, Groenewegen, & Kolb, 2003). The perturbational effects of ADMs on rodent mPFC monoamine levels may correspond to their perturbational effects in human brain regions implicated in depression, such as the VLPFC. Unless otherwise indicated, we rely on microdialysis studies in which a single dose in the 10-15mg/kg range was systemically administered (either by intraperitoneal injection or oral administration). This dose range is commonly used and approximates clinically relevant doses (Koch et al., 2003). From these studies, we extracted the average percent increase of each monoamine (5-HT, NE, and DA) above baseline in the mPFC (see Table 1).

Microdialysis studies of mPFC monoamine levels can be found for most of the major standalone ADMs used in discontinuation studies. However, we lack mPFC microdialysis data for the two monoamine oxidase inhibitors (MAOIs)—phenelzine and selegiline—that have been

used in discontinuation studies. Phenelzine is a dual MAO-A/B inhibitor, and so is selegiline at the doses used in the discontinuation study (Stahl, 2008). As noted above, the inhibition of MAO-A primarily increases 5-HT and NE. Although MAO-B does not metabolize 5-HT or NE, it does metabolize β-phenylethylamine, which is related to the release of catecholamines, including 5-HT and NE (Kitaichi et al., 2010). The inhibition of MAO-B can therefore indirectly increase 5-HT and NE as well as directly increase DA (Kitaichi et al., 2010).

Of the ADMs, dual MAO-A/B inhibitors exert the most powerful effects on monoamine levels. Due to differences in regional effects of ADMs, many ADMs do not increase monoamine levels when averaged across the whole rodent brain, yet dual MAO-A/B inhibitors are powerful enough to do so (Bano, Gitay, Ara, & Badawy, 2010; Campbell & Marshall, 1974; Fuller, Perry, & Molloy, 1974; Renard, Dailly, Nic Dhonnchadha, Hascoet, & Bourin, 2004). In one study, a single dose of phenelzine increased whole brain levels of 5-HT by 240%, NE by 150%, and DA by 170% (Parent, Habib, & Baker, 2000).

In mPFC, dual MAO-A/B inhibitors tend to have greater effect than the whole brain average. The inhibition of MAO-A by itself increases mPFC levels of 5-HT and NE by 200-300% (Bel & Artigas, 1995; Finberg, Pacak, Kopin, & Goldstein, 1993), but the simultaneous inhibition of MAO-A and MAO-B causes increases of at least 400% (Bel et al., 1995; Kitaichi et al., 2010; Takahashi, Takada, Nagai, Urano, & Takada, 2000). We therefore conservatively assume that phenelzine and selegiline (at dual inhibition doses) increase mPFC monoamine levels by 400% above baseline (Table 1). However, since we do not have precise mPFC measurements for phenelzine and selegiline, for our analyses we capped the maximum perturbational impact of ADMs at 400%. We label the perturbational effect of a drug for each monoamine as follows: p5HT (for serotonin), pNE (for norepinephrine), and pDA (for dopamine).

Table 1. Perturbational effects of antidepressants on mPFC levels of monoamine neurotransmitters (expressed as percent over baseline).

ADM	p5HT	pNE	pDA	ADM Class	References
Phenelzine	400	400	400	MAOI	See text
Selegiline	400	400	400	MAOI	See text
Desvenlafaxine	250	230	167	SNRI	See text
Duloxetine	195	270	200	SNRI	(Kihara & Ikeda, 1995; Koch et al., 2003)
Milnacipran	94	147	119	SNRI	(Marien, Floutard, & Ladure, 2007)
Venlafaxine	250	230	167	SNRI	(Koch et al., 2003; Weikop, Kehr, & Scheel-Kruger, 2007)
Citalopram	466	90	71	SSRI	(Bymaster et al., 2002)
Escitalopram	466	90	71	SSRI	See text
Fluoxetine	368	189	150	SSRI	(Bymaster et al., 2002)
Fluvoxamine	255	121	102	SSRI	(Bymaster et al., 2002)
Paroxetine	364	86	103	SSRI	(Bymaster et al., 2002)
Sertraline	438	117	116	SSRI	(Bymaster et al., 2002)
Amitriptyline	100	200	175	TCA	(Kihara et al., 1995)
Clomipramine	150	200	320	TCA	(Koch et al., 2003; Tanda, Carboni, Frau, & Dichiara, 1994)
Desipramine	100	210	250	TCA	(Seo et al., 1999; Tanda et al., 1994)

Imipramine	175	300	200	TCA	(Jordan, Kramer, Zukas, Moeller, & Petty, 1994)
Nortriptyline	100	200	175	TCA	See text

The perturbational effects of other ADMs generally correspond to the class to which they belong, but there are exceptions and, more importantly, differences in degree. The selective serotonin reuptake inhibitors (SSRIs) selectively bind to the serotonin transporter, and so they tend to increase cortical levels of serotonin. The effects of citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline on mPFC monoamine levels were assessed in a single study (Bymaster et al., 2002). Fluoxetine is unique among the SSRIs in that it also increases NE and, to a lesser extent, DA in the mPFC (Bymaster et al., 2002; Stahl, 2008). The mechanism is not by reuptake blockade, but by antagonism of 5-HT_{2C} receptors (Stahl, 2008). While we lack microdialysis data for escitalopram in the 10-15mg/kg range, escitalopram is the active S-enantiomer of citalopram (Stahl, 2008), so we use the same perturbational values as for citalopram.

The serotonin norepinephrine reuptake inhibitors (SNRIs) selectively bind to both the 5-HT and NE transporters, although, as a class, they tend to have greater affinity for the 5-HT transporter than the NE transporter. ADMs that inhibit NE reuptake also tend to increase prefrontal levels of DA to some degree because there are few DA transporter molecules in the prefrontal cortex, so DA has a tendency to diffuse widely from the synapse (Stahl, 2008). DA eventually gets taken back into neurons by the NE transporter, which has a higher affinity for DA than NE (Stahl, 2008). We relied on several studies (Kihara et al., 1995; Koch et al., 2003; Marien et al., 2007; Weikop et al., 2007) to get data on the mPFC monoamine effects of the SNRIs used in discontinuation studies—desvenlafaxine, duloxetine, milnacipran, and venlafaxine. Venlafaxine does not have much effect on NE at 15mg/kg, but it has a larger effect at 40mg/kg (Koch et al., 2003). The discontinuation studies of venlafaxine use doses that are much higher than the recommended dose, so we use the data for 40mg/kg. We lacked microdialysis data for desvenlafaxine, but it is the active metabolite of venlafaxine (Stahl, 2008). In the discontinuation study of desvenlafaxine, it was also administered at doses that are much higher than the recommended dose, so we use the same perturbational values as for venlafaxine.

The tricyclic antidepressants (TCAs) also bind to the 5-HT and NE transporters, although, as a class, they tend to have greater affinity for the NE transporter. We relied on several studies (Bongiovanni, Newbould, & Jaskiw, 2008; Jordan et al., 1994; Kihara et al., 1995; Koch et al., 2003; Tanda et al., 1994) to get data on the mPFC monoamine effects of the TCAs that have been used in discontinuation studies—amitrityline, clomipramine, desipramine, imipramine, and nortriptyline. We lacked microdialysis data for nortriptyline, but since it is the active metabolite of amitryptiline, we assigned it the same perturbational values.

Study overview

To summarize, we conduct a meta-analysis to test two predictions of the hypothesis that monoamine levels are under homeostatic control in patients diagnosed with MDD. First, patients who remit with ADM treatment will have a higher risk of relapse after treatment stops than patients who remit without ADM treatment. Second, the risk of relapse after ADM treatment is discontinued will be positively related to the perturbational effects of the ADM on prefrontal monoamine levels.

Two types of studies are relevant to these predictions. In ADM extension studies, patients diagnosed with MDD are initially randomly assigned to ADM or placebo during the treatment phase, and then remitters in both groups are followed in an extension phase in which they continue to receive the same treatment. Since our first prediction relates to the risk of relapse after remission without ADM treatment, we only consider the Placebo-Placebo arms of extension studies. We put placebo in its own class (PBO) and assign to placebo treatment a perturbational score of 100 (no effect on baseline levels) for each of the monoamines.

In ADM discontinuation studies, all patients diagnosed with MDD go through an initial ADM *treatment phase* and then remitters go through a *discontinuation phase* in which they are randomly assigned, under double-blind conditions, to either continued treatment (Drug-Drug) or placebo (Drug-Placebo). Since our second prediction deals with the risk of relapse after ADM discontinuation, we only consider the Drug-Placebo arms of discontinuation studies.

In our meta-analysis, we include all the randomized, double-blind, placebo-controlled ADM extension studies we can find since patients in the Placebo-Placebo arms of these studies have not received any pharmacological treatment. However, we limit analysis to ADM discontinuation studies in which patients receive chronic treatment of a single ADM from one of the major standalone classes—the MAOIs, the TCAs, the SNRIs, or the SSRIs. As a practical matter, microdialysis data on the mPFC monoaminergic effects of ADMs from outside these classes is limited.

Study selection

Design of relevant studies

Studies included in our meta-analysis had to meet several design criteria. First, patients must have had a primary diagnosis of an episode of unipolar major depression (MDD, recurrent or chronic, with or without dysthymia). A variety of diagnostic methods were allowed. Additionally, most published studies excluded depressed patients who had a diagnosis of bipolar disorder or concurrent alcohol or substance abuse. We therefore excluded studies specifically focusing on these special populations. We did not exclude studies in which patients were diagnosed with other comorbid conditions, such as anxiety disorder or diabetes (Lustman et al., 2006) provided they met all other criteria.

Second, each study had to have an initial period of ADM treatment followed by randomization to continued treatment with ADM or placebo under double-blind conditions. We allowed studies with multiple treatment phases, provided ADM treatment was continuous from the beginning of the study until discontinuation.

Third, we excluded any study that did not involve at least one of the major ADM classes—MAOI, TCA, SNRI, or SSRI.

Fourth, we excluded any study in which multiple ADMs from different classes were simultaneously administered to the same individuals because we were interested in isolating the

effects of individual drug classes. We did not allow the sequential administration of different ADMs, because they have different perturbational effects.

Fifth, we excluded any study in which patients also received psychotherapy because it has been shown to influence relapse rates after discontinuation.(Hollon, Stewart, & Strunk, 2006)

Sixth, to avoid double-counting, we excluded any report that was a re-analysis of data already included in the analysis.

We included part of a study in which patients were given fluoxetine for 12 weeks and then randomized to one of four branches (Reimherr et al., 1998): (1) placebo for the duration of the study; (2) continued treatment with fluoxetine for 14 weeks before assignment to placebo; (3) continued treatment with fluoxetine for an additional 36 weeks followed by placebo; and (4) continued treatment with fluoxetine for the duration of the study. We include the relapse results from only the first assessment period (12 weeks after randomization), because this was the only assessment in which all subjects in the placebo group had been treated with fluoxetine for the same period of time.

We excluded another study (Eric, 1991) because it was a conference abstract that provided a preliminary report of an ongoing study. Consequently, important information was missing (e.g., average age, proportion of patients who were women), and it appeared to be a preliminary report of a later published study (Montgomery et al., 1993a).

Search strategy

Our search strategy involved two steps. First, we used four meta-analyses of discontinuation studies (Geddes et al., 2003; Glue et al., 2010; Kaymaz et al., 2008; Viguera et al., 1998) and a recent meta-analysis of extension studies (Zimmerman, Posternak, & Ruggero, 2007) that used rigorous search criteria as baseline sources. Second, we conducted searches of the Web of Science database covering 1965 until October, 8, 2010. To search for discontinuation studies, we used the keywords “antidepress* & placebo & (relapse or recurren*) & (discontinu* or mainten* or continua*)”. Then, we conducted similar searches substituting specific drugs for “antidepress*” (e.g, “sertraline”, “phenelzine”, “amitriptyline”, etc.). To search for extension studies, we used the keywords “antidepress* & placebo & (relapse or recurren*) & (mainten* or continua*) & extension”. The flow diagram for the search procedure is in Figure 1.

[insert Figure 1 here]

Variables

From each study, we extracted information on a number of variables that were either directly relevant to our hypotheses, or were important covariates to control for.

Demographic variables (age, sex)

We coded each study for the average age of patients (variable name=*age*), and for the proportion of patients who were women (variable name=*sex*), who were randomized to placebo. Two studies did not report the average age or sex composition of the patients randomized to placebo (Doogan & Caillard, 1992; Montgomery, Rasmussen, & Tanghoj, 1993b), so we took the demographic characteristics of all those who were subject to randomization instead (Doogan et al., 1992; Montgomery, Rasmussen, Lyby, Connor, & Tanghoj, 1992). Five studies did not report any information on the age of the sample, and two of these studies did not provide any information on the sex composition of the sample (see Appendix A).

Depression history (dephx)

In principle, people with greater histories of depression could be at a greater risk of relapse (Kendler, Thornton, & Gardner, 2000). We therefore coded each study for the minimum number of prior episodes required for entry into the study (variable name=*dephx*). Where not reported, we assumed no restriction.

Treatment resistance (txresist)

In principle, patients who are more resistant to pharmacological treatment could be at greater risk of relapse (Rush et al., 2006). We therefore coded each study for whether treatment resistant patients were targeted. Studies were coded as involving treatment resistant patients if they included hospitalized patients, or targeted patients with chronic or atypical depression (variable name=*txresist*).

Drug variables (class, halflife)

Characteristics of ADMs other than their perturbational effects on mPFC monoamine levels could, in principle, be predictors of the risk of relapse. The elimination half-life of the drug is thought to be pharmacologically important, so we included it in some of our analyses (variable name=*halflife*). We do not use the half-lives of phenelzine or selegiline as they irreversibly bind to monoamine oxidase, so effects may last for two weeks after discontinuation (Lemke, Williams, Roche, & Zito, 2010). We took all half-life values from Sadock and Sadock (Sadock & Sadock, 2005), using the value of the parent compound or its longest acting active metabolite. Where a range in half-life was reported, we took the midpoint.

Table 2. Half-lives of different antidepressant drugs.

Drug	Class	Half-life (hrs)
Milnacipran	SNRI	8
Venlafaxine	SNRI	10
Desvenlafaxine	SNRI	10
Duloxetine	SNRI	12
Imipramine	TCA	17.5
Fluvoxamine	SSRI	19.5
Desipramine	TCA	20
Paroxetine	SSRI	21
Amitriptyline	TCA	25

Escitalopram	SSRI	29.5
Citalopram	SSRI	35
Clomipramine	TCA	37.5
Nortriptyline	TCA	37.5
Sertraline	SSRI	83
Fluoxetine	FLX	240

Treatment duration (txdur)

The duration of acute treatment with an ADM before transition to placebo could potentially be an important predictor of the risk of relapse, as discussed in the introduction. Ideally, each study would have a clearly defined treatment period, which is the time from the onset of ADM initiation to randomization to placebo (variable name=*txdur*). Unfortunately, patients were subjected to treatment for varying time periods in three of the MAOI studies (Davidson & Raft, 1984; Harrison et al., 1986; Stewart, Tricamo, McGrath, & Quitkin, 1997) and four of the TCA studies (Cook, Helms, Smith, & Tsai, 1986; Coppen et al., 1978; Mindham, Howland, & Shepherd, 1973). For these studies, we used the average treatment period or the midpoint in the range. For one TCA study, the only information available was that acute treatment persisted for 6 weeks after remission of the index episode (Coppen et al., 1978). Since there is a therapeutic delay of several weeks for all ADMs, we assumed a treatment period of 10 weeks. Time periods are usually reported in weeks. We convert this time to 30-day months. Often, time periods of 24 weeks are referred to as being equal to 6 months, which only makes sense if months are considered four week periods. For this reason, when time periods are reported in months, we assume that each month is equal to 4 weeks.

Dropout rate during Treatment (droprate)

Patients may drop out of discontinuation and extension studies, most commonly because they fail to remit or because they have adverse effects from the treatment. This could be an important covariate influencing the relapse rate. In principle, the people who drop out could be more vulnerable to relapsing, leaving patients who remain in the sample more resistant to relapse. We calculated the proportion of patients who dropped out of each study during the treatment phase as the number of patients who dropped out divided by the total number of patients who entered the study (variable name=*droprate*). Ten studies lacked information on dropout rate (see Appendix A).

Relapse risk period (riskper)

The studies also varied in the period of time after randomization to placebo during which patients were to be monitored for relapse. This could be an important predictor of relapse, with longer monitoring periods associated with a greater risk of relapse. As with treatment duration, this is often reported in weeks. We convert such time periods into 30-day months. When reported in months, we assumed that each month was equivalent to 4 weeks.

Stringency of criteria for defining depressive relapse (stringency)

We do not distinguish between patients who experienced a recurrence (onset of a new episode) from those who relapsed back into their index episode. For consistency, we refer to all lapses of remission as relapses, though some may be recurrences.

As discussed in the introduction, the stringency of criteria used to define a relapse (hereafter, *stringency*) should be an important negative predictor of the relapse rate. Commonly used tools for assessing depressive symptoms included the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), the Clinical Global Impression–Improvement (CGI-I) or –Severity (CGI-S) scales (Guy, 1976), the Montgomery-Asberg Depression Research Scale (Montgomery & Asberg, 1979), DSM-III or DSM-IV criteria, the Beck Depression Inventory (Beck & Beamesderfer, 1974), or clinical judgment. Researchers could vary on the number of these assessment tools and the cutoff scores used to diagnose a relapse. Additionally, researchers varied on the duration of time that symptoms must persist.

Taking into account the stringency of relapse criteria is difficult as the variety of qualitatively different criteria prohibits easy comparison. However, there are strong a priori reasons to believe that stringency must be an important variable that affects relapse rates. Simply put, the more stringent the criteria that a study uses to define a relapse, the more difficult it will be for patients to meet the criteria, and overall relapse rates should be lower.

We operationalize stringency as the number of assessment hurdles that must be passed for an episode to be deemed a relapse. This has the drawback of ignoring cutoff differences. Thus, a study that defines relapse as requiring a HRSD>18 would be given the same stringency score as a study that requires a HRSD>12. However, there are very few studies that could be directly compared solely on the basis of differences in cutoff scores, so it is an impractical metric.

The advantage of using the number of assessment hurdles is that it is an objective way for us to compare the studies, and it leads to a natural way of taking into account differences in the requirements for duration of symptoms. For instance, if a study defines a relapse as requiring a HRSD>15 and a CGI-S>3 for two weeks in a row, then we assign it a stringency rating of four (one HRSD assessment and one CGI-S assessment must be passed each of the two weeks). When a study uses a number of criteria paths by which a patient can be designated as relapsed, we give priority to the path with the shortest duration requirement, then to the path with the fewest number of assessments that must be passed.

Two of the authors, PWA and LJH, independently rated each study for the stringency of the relapse criteria. Agreement between the two ratings was very high: kappa=0.782, weighted kappa=0.903, and tetrachoric correlation=0.986. Differences between the two ratings were then reconciled.

Nearly all the studies had stringency scores ranging from 1-4. However, two studies used a complex combination of assessments and symptom duration requirements (Amsterdam & Bodkin, 2006; Keller et al., 1998). Using our strict definition for the number of assessment hurdles that must be passed, one study (Amsterdam et al., 2006) would receive a rating of 8 (2 for the number of weeks that DSM-IV criteria must be satisfied, 2 for the number of weeks that

HRSD>13, 2 for the number of weeks that patients must have CGI-S≥3, and 2 for the number of weeks that the CGI-S score must be elevated by 2 points above the baseline score). The other study (Keller et al., 1998) would receive a rating of 11 (4 for the number of weeks that DSM-IV criteria must be satisfied, 2 for the number of weeks that patients must have a CGI-S≥4, 2 for the number of weeks that a patient must have a CGI-I≥3, 2 for the number of weeks that there must be a 4 point increase in HRSD score over that of the maintenance phase, and 1 for confirmation by a senior investigator). These studies are clearly outliers. Moreover, retaining these scores could be misleading if some of the additional hurdles were redundant and had little impact on relapse rates. We therefore considered a range of stringency scores of 5-8 for these studies, with the minimum value reflecting the fact that their relapse definitions were more stringent than those of other studies. All reported results are based on stringency scores of 5. Unless otherwise stated, results do not change appreciably with different stringency scores.

Relapse rate (relrate)

We calculated the relapse rate (variable=*relrate*) as the proportion of patients who had been randomized to placebo who satisfied relapse criteria over the relapse risk period. It was not uncommon for the authors of a study to report in the text of the paper a relapse number that was lower than the number that could be derived from the Kaplan-Meier survival curve (Hochstrasser et al., 2001; Montgomery et al., 1993b; Rickels et al., 2010; Robert & Montgomery, 1995). This occurred because the study authors were, for some reason, analyzing relapse disparities between the Drug-Drug and Drug-Pla groups at a time point before the end of the relapse risk period. This may not have been an unreasonable thing to do for those studies, but for the purposes of this analysis it is important to understand precisely how many relapses occurred over a specific interval. In such situations, we took the relapse number from the Kaplan-Meier survival curves for the relapse risk period that the authors reported in their study.

Imputation of Missing Values

As discussed above, some studies did not provide information about the average age, sex composition, or the dropout rate during acute treatment. We assumed that this data were missing at random, which means that the missing data may depend on variables that are known, but not on unknown variables. Under such circumstances, it is reasonable to use multiple regression to impute the missing data based on the data for which information is available (Little & Rubin, 1989), which we did using IVEware for SAS (Raghunathan, Solenberger, & Van Hoewyk, 2002). We used the following variables to impute values: year in which the report was published, txresist, dephx, stringency, the specific antidepressant, ADM class, the perturbational scores for each of the monoamines in mPFC, relapse rate, txdur, and riskper.

Often, a missing data point represents a person about whom a piece of information is missing. In this case, imputation involves using regression to predict the unknown information based on all the known information in the entire sample plus a stochastic element to represent the fact that the missing information cannot be predicted with certainty. However, in our situation, a missing data point is not an individual but a study in which a summary statistic—the average age, sex composition, or dropout rate—is missing. We want to impute the missing summary statistics (rather than the missing data of an individual) based on the summary statistics from all

the studies that were available. However, imputing with a stochastic component would introduce far more variability into the summary statistic than actually existed. For this reason, we imputed without stochasticity. Due to the non-stochasticity, the estimates for analyses in which imputed data were used are slightly more precise (their standard errors are smaller) than they should be. However, since age, sex, and dropout rate were not significant predictors of the relapse rate, this problem would not apply to our best fitting model.

Statistical analysis

We conducted weighted least squares regression analyses using PROC REG in SAS on both the non-imputed and the imputed datasets. Since the results were not significantly different, we only report the results from the imputed data. All studies were weighted by the inverse of the variance for the proportion of patients with a relapse during the discontinuation phase. To avoid over-fitting problems that can arise from having more variables than studies, we constructed a best fitting model. We did this by examining how the removal of each variable influenced the adjusted R^2, keeping all the other variables in the model. We then eliminated the one variable that improved the fit the most. This procedure was repeated with the remaining variables until all model variables were significant or their elimination could not improve the fit. In all reported models, the results have been examined for, and are unaffected by, influential data points. No reported models showed signs of over-fitting.

Results

Forty six papers met inclusion criteria, constituting 49 samples and 3,454 patients (Alexopoulos et al., 2000; Amsterdam et al., 2006; Anton et al., 1994; Bremner & Smith, 1996; Cheung et al., 2008; Claghorn & Feighner, 1993; Coppen et al., 1978; Davidson et al., 1984; Detke et al., 2004; Dobson et al., 2008; Doogan et al., 1992; Emslie et al., 2008; Entsuah, Rudolph, Hackett, & Miska, 1996; Georgotas, Mccue, & Cooper, 1989; Gilaberte et al., 2001; Gorwood, Weiller, Lemming, & Katona, 2007; Harrison et al., 1986; Hochstrasser et al., 2001; Kamijima, Burt, Cohen, Arano, & Hamasaki, 2006; Keller et al., 1998; Klerman, Dimascio, Weissman, Prusoff, & Paykel, 1974; Klysner et al., 2002; Kocsis et al., 1996; Kocsis et al., 2007; Lustman et al., 2006; McGrath et al., 2006; Montgomery et al., 1988; Montgomery et al., 1993a; Montgomery et al., 1993b; Montgomery, Reimitz, & Zivkov, 1998; Montgomery, Entsuah, Hackett, Kunz, & Rudolph, 2004; Perahia et al., 2006; Perahia et al., 2009; Reimherr et al., 1998; Reynolds et al., 1999; Rickels et al., 2010; Robert et al., 1995; Robinson et al., 1991; Rouillon et al., 2000; Schmidt, Fava, Robinson, & Judge, 2000; Simon, Aguiar, Kunz, & Lei, 2004; Stein, Rickels, & Weise, 1980; Stewart et al., 1997; Terra & Montgomery, 1998; van Praag & de Haan, 1980; Wilson, Mottram, Ashworth, & bou-Saleh, 2003). The information extracted from each study is listed in Appendix A. In Figure 2, we provide a forest plot of the relapse rates of individual studies, grouped by the particular ADM used, and ADMs from the same class are grouped together in order of increasing stringency.

[insert Figure 2 here]

Table 3 provides basic summary statistics. The PBO studies had the lowest unadjusted relapse rate, which is consistent with our first prediction. However, this is also consistent with

the possibility that the PBO studies tended to include patients with a lower risk of relapse (e.g., patients were less likely to have a prior history of depression, or they were more resistant to pharmacological treatment). Moreover, the PBO studies had the highest dropout rate during acute treatment, while the ADM classes had similar dropout rates. The dropout rate pattern suggests a potential selection bias problem for the PBO group, so we include the dropout rate as a covariate in all our regression analyses, unless otherwise specified. The SSRI studies had the second highest raw relapse rate, after the TCAs, while the MAOIs had the second lowest raw relapse rate of the ADM classes.

Table 3. The number of samples (N), the dropout rate during the treatment phase, and the relapse rate after randomization to placebo for each ADM class.

Class	N	% Dropout (Treatment)	# Patients on Placebo	# Patients who Relapsed	% Relapse
PBO	7	65.4[a]	437	108	24.7
SSRI	19	49.0	1,526	743	48.7
SNRI	7	47.7	962	404	42.0
TCA	9	46.5[b]	178	99	55.6
MAOI	6	51.6[c]	218	99	45.4
Overall	49	51.2[d]	3,454	1,453	42.1

[a] Based on 5 of the 7 samples
[b] Based on 5 of the 9 samples
[c] Based on 2 of the 6 samples
[d] Based on 39 of the 49 samples

Correlations

For the ADM discontinuation studies, we examined the bivariate correlations between the continuous and count variables (Table 4). The perturbational effects of NE and DA are both significantly correlated with the relapse rate, but the correlation between pNE and pDA approaches unity, indicating a collinearity problem. The perturbational effect of 5-HT is not significantly correlated with the relapse rate, but it is related to other variables that could be potential confounds (risk period, treatment duration). Partially consistent with our prediction, there is a marginally significant, negative correlation between the stringency variable and the relapse rate. The stringency variable also shows a marginally significant relationship between the risk period and treatment duration, suggesting that they could be potential confounds for each other. Finally, the risk period and treatment duration are significantly correlated with each other, suggesting that they could also be potential confounds for each other.

Table 4. The bivariate correlations between the continuous and count variables.

	1	2	3	4	5	6	7	8	9	10
1. p5HT	1									
2. pNE	-0.15	1								
3. pDA	-0.09	0.94[d]	1							
4. Age	-0.06	-0.12	-0.10	1						
5. Sex	0.01	-0.05	-0.02	0.13	1					
6. Droprate	0.02	0.17	0.14	-0.12	-0.14	1				
7. Riskper	-0.30[†]	0.02	0.07	0.44	0.04	-0.03	1			
8. Txdur	-0.18	0.20	0.14	0.19	-0.18	0.24	0.48[b]	1		

9. Stringency	-0.02	0.18	0.14	0.00	-0.03	0.15	0.28[†]	0.32[a]	1	
10. Relrate	0.07	0.53[c]	0.60[d]	0.00	-0.11	0.14	0.12	0.12	-0.30[†]	1

[†] p<0.10, [a] p<0.05, [b] p<0.01, [c] p<0.001, [d] p<0.0001

Predictors of the dropout rate

To formally test whether there is a potential selection bias problem in the PBO group due to a higher dropout rate during acute treatment, we regressed the dropout rate on the ADM classes and tested for a formal contrast of the ADM classes against the PBO class. We included as covariates the average age, the proportion of patients who were female, the duration of acute treatment, whether treatment resistant patients were targeted in the study, and the minimum number of depressive episodes required for entry. The contrast was significant, p=0.003, indicating that the ADM classes had lower dropout rates than the PBO group. Additionally, the duration of acute treatment was a positive predictor of dropout rate, β=+0.023, SE=0.010, p=0.03. Subsequent analysis showed that it was driven by the ADM classes (not the PBO class), suggesting that longer drug treatment caused higher dropout, possibly due to adverse drug effects. In short, these results suggested that there could be a potential selection bias problem in the PBO studies.

Does the dropout rate predict the relapse rate?

Next, we regressed the relapse rate on the dropout rate to see whether the potential selection bias problem was affecting the relapse rate. By itself, dropout rate was not a significant predictor, β=-0.213, SE=0.225, p=0.35. We then added covariates (age, sex, txresist, txdur, dephx), but the dropout rate was still not significant, β=-0.262, SE=0.257, p=0.32.

Even though we had no evidence that the dropout rate—by itself or in conjunction with covariates—was a predictor of the relapse rate, we included it as a covariate in our subsequent analyses unless otherwise indicated. We also included the interaction of dropout rate with a binary treatment variable (PBO or ADM), but it was not significant in any of the analyses, so we do not report it.

Does the stringency variable negatively predict the relapse rate?

The correlational results suggested that the stringency of relapse criteria could be an important negative predictor of the relapse rate. To give a visual presentation of this, we graphed the relapse rate as a function of the stringency variable for each class (see Figure 3). Within each class, the relapse rates tend to decline with stringency, suggesting that stringency is an important covariate. Moreover, the MAOIs have the highest relapse rates at each level of stringency. It is only for a stringency score of 5 or greater that the MAOI relapse rate drops off substantially. This is actually due to a single study (Amsterdam et al., 2006) with the second highest score on the stringency variable in our meta-analysis (stringency score=8). Comparison of this figure with Table 3 suggests that, consistent with our second prediction, the ADMs with the greatest perturbational effects may actually have the highest relapse rates, but these can be obscured if one does not take the stringency of relapse criteria into account. To help illustrate this point further, we separated out the fluoxetine (FLX) studies from the other SSRIs. As discussed above, fluoxetine is unique among the SSRIs in that it causes NE and DA to increase in the mPFC

through a mechanism other than reuptake blockade, which makes it substantially more perturbational than other SSRIs. Consistent with our second prediction, the fluoxetine studies tend to have higher relapse rates than the other SSRIs. In fact, the relapse rates of the fluoxetine studies seem to be more comparable to that of the SNRI and TCA studies—other ADM classes that influence NE and DA.

[insert Figure 3 here]

To formally test our prediction, we regressed the relapse rate on the stringency variable. The stringency variable, by itself, is only a marginally significant negative predictor of the relapse rate when all 49 samples are analyzed, β=-0.035, SE=0.018, p=0.06. However, it reaches significance when only the 42 ADM discontinuation samples are analyzed, β=-0.057, SE=0.017, p=0.002. It also reaches significance in the entire sample when covariates (age, sex, txresist, dephx, droprate, txdur, riskper) are included, β=-0.050, SE=0.019, p=0.01.

Does the PBO group have a lower relapse rate than the ADM classes?

Our first prediction was that the PBO group would have a lower relapse rate than that of the ADM studies, and this was supported by the summary statistic results. To formally test this, we constructed a binary treatment variable (0=PBO, 1=the ADM classes). We then regressed the relapse rate on this treatment variable. The treatment variable was significant, β=0.277, SE=0.067, p=0.0001, indicating that the PBO group had a significantly lower relapse rate than the ADM classes. Inclusion of the stringency variable only increased the significance of the results. As discussed above, the lower relapse rate of the PBO group could be due to a selection bias problem in which more relapse-vulnerable patients dropped out during acute treatment, or because more patients in the PBO studies were more vulnerable to relapse at the outset. To formally test this, we included as covariates the minimum number of depressive episodes required for entry into the study, whether treatment resistant patients were targeted, and the dropout rate during the acute treatment phase. None of the sample characteristic variables were significant, while the treatment variable remained significant, β=0.342, SE=0.080, p=0.0001. The inclusion of other covariates also did not influence the significance of this variable.

Do the perturbational properties of ADMs predict the relapse rate?

Our second prediction was that the perturbational properties of ADMs on mPFC monoamine levels would be positive predictors of the relapse rate. To formally test this, we regressed the relapse rate on the perturbational effects on 5-HT and NE. (Since the perturbational effects on NE and DA are highly collinear, we do not analyze them at the same time.) We included as covariates average age, the proportion of women in the sample, the minimum number of prior episodes required for entry, whether treatment resistant patients were targeted, the dropout rate during acute treatment, the duration of acute treatment, the length of the risk period, and the stringency of relapse criteria. We report the estimates of this model in Table 5, Model I. The perturbational effects of ADMs on 5-HT and NE were both significant positive predictors of the relapse rate, as was stringency and the duration of the risk period.

Table 5. Parameter estimates and standard errors (SE) from the weighted least squares analyses (see text)

	Model I			Model II	Model III	
Variables	**Estimate**	**SE**	**95% CI**	**Estimate**	**Estimate**	**SE**
p5HT	0.00063[b]	0.00018	0.00026, 0.00099	0.00043[†]	0.00061[c]	0.00016
pNE	0.0011[d]	0.00024	0.00065, 0.0016	0.0010[c]	0.0012[d]	0.00022
Age	-0.0015	0.0024	-0.0065, 0.0035	-0.00013		
Sex	-0.00063	0.0023	-0.0052, 0.0040	-0.0036		
Txresist	-0.022	0.0604	-0.144, 0.100	-0.0267		
Dephx	0.0087	0.0382	-0.0687, 0.0860	0.0293		
Droprate	-0.0449	0.1928	-0.4352, 0.3455	0.2448		
Txdur	0.0176	0.0144	-0.0116, 0.0468	0.0085		
Riskper	0.0091[a]	0.0043	0.00042, 0.0178	0.0049[†]	0.0114[c]	0.0031
Stringency	-0.1025[d]	0.0179	-0.1386, 0.0664	-0.1062[d]	-0.0946[d]	0.0161
R^2		0.618			0.586	
Adj. R^2		0.518			0.548	

[†] $p<0.10$, [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$, [d] $p<0.0001$

Next, we excluded the PBO studies and re-ran the analyses, the results of which are in Table 5, Model II. Comparing Model II with Model I shows that the estimates for Model II are well within the 95% confidence limits of the estimates for Model I. Thus, including the PBO studies does not fundamentally change the parameter estimates—they only increase the power.

Then, we included the PBO studies and excluded the MAOI studies, to determine how the parameter estimates were affected by the MAOI studies. The estimates for this model (not shown) were also well within the 95% confidence limits of the Model I estimates. Additionally, the perturbational variables for 5HT and NE, and the risk period and stringency variables, were all statistically significant. Thus, the inclusion of the MAOI studies also does not fundamentally change the parameter estimates.

Using the entire sample, we report the best-fitting model in Table 5, Model III. Only the perturbational variables for 5-HT and NE, the stringency variable, and the risk period remained in the model, but they still explained nearly 60% of the variance.

Finally, we re-ran each of these analyses using the perturbational variable for DA in place of NE (results not shown). They all fit nearly as well, as might be expected from their collinearity.

Discussion

We found robust support for our predictions. The risk of relapse after ADM discontinuation was higher than the risk of relapse after remission on placebo. Moreover, the risk of relapse was after ADM discontinuation was positively predicted by the degree to which ADMs perturbed 5-HT and NE levels in the rodent mPFC. The risk of relapse was also positively predicted by the degree to which ADMs perturbed DA levels in the mPFC. Given the high degree of collinearity between the perturbational effects of ADMs on NE and DA, we prefer the 5-HT/NE model over the 5-HT/DA model because the evidence for the involvement of NE in depression is stronger.

While the results are robust, their implications depend on their interpretation, so we first discuss several potential confounds. Is it possible, for instance, that the results do not reflect the risk of relapse, but rather withdrawal symptoms? The discontinuation of antidepressant medication can cause withdrawal symptoms (also known as discontinuation syndrome) that are unrelated to relapse, but may sometimes be mistaken for relapse (Haddad, 1997). Such mistakes are more likely with untrained physicians (Haddad, 1997), so it should be less of a problem in ADM discontinuation studies where trained psychiatrists are employed to evaluate putative cases of relapse. Regardless, drugs with longer half-lives are less likely to show discontinuation syndrome (Fava, 2006; Michelson et al., 2000). If discontinuation syndrome were being mistaken for relapse, then drugs with longer half-lives should have *lower* relapse rates. To test this possibility, we added half-life to the best-fitting model and eliminated the perturbational variables (results not shown). The resultant model did not fit as well, and, in fact, half-life was a significant *positive* predictor of relapse rate. This is because drugs with stronger perturbational effects on 5-HT tend to have longer half-lives. We therefore have no evidence that withdrawal symptoms were mislabeled as relapses.

There is some evidence that ADM treatment resistant patients may have higher relapse rates (Rush et al., 2006). Is it possible that studies using ADMs with stronger perturbational properties had higher relapse rates, not due to the pharmacological properties of the drugs used, but because they also had higher proportions of treatment resistant patients participating in them? There are two ways this could happen. First, studies using stronger ADMs could have been more likely to target treatment resistant patients at the outset. Second, the characteristics of patient samples in discontinuation studies may change during treatment due to dropouts caused by the treatment, causing a potential selection bias problem.

A related issue is whether the PBO class (denoted by the Placebo-Placebo arms of the extension studies) was fundamentally different from the other classes (denoted by the Drug-Placebo arms of the ADM discontinuation studies). For instance, perhaps the PBO studies targeted fundamentally different samples at the outset, or perhaps they had higher dropout during the acute treatment phase so that patient populations were substantially different by the beginning of the extension phase. Consistent with this, the PBO studies did have a higher dropout rate and a lower relapse rate than the ADMs as a group. Of course, this result might also be expected if the PBO studies were quantitatively different only because they were on one end of the perturbational continuum.

To deal with these issues in our analyses, we included two variables as covariates that captured differences in the initial patient populations: whether treatment resistant patients were being targeted, and the minimum number of depressive episodes required for entry into the study. Neither variable was significant in any of our analyses, and their inclusion did not change the statistical significance of any result. We also included the dropout rate during acute treatment because the PBO studies had significantly higher dropout rates, and the dropout rate in the ADM discontinuation studies was positively associated with the duration of treatment. Both findings suggested that the dropout rate during treatment might be a proxy for the degree of selection bias at discontinuation. If selection bias problems were driving the lower relapse rate in the PBO studies or the relationship between relapse rate and perturbational variables, then dropout rate during the treatment phase could predict relapse, either as a main effect or in interaction with binary treatment status (Placebo vs. Drug). Neither term was significant in any of our analyses, nor did they affect the significance of any result.

In any event, the strongest reason for inferring that the PBO studies were not qualitatively different from the other studies is that excluding them did not significantly change the parameter estimates of any variables, including the perturbational variables. This suggests that the PBO studies simply anchor one end of the perturbational continuum and increase the power of our analyses. (Similarly, even though we had to make assumptions about the prefrontal perturbational effects of phenelzine and selegiline based on evidence from other dual MAO-A/B inhibitors, our results did not change significantly if we excluded the MAOI studies.)

Another potential confound is that we are only using published studies in our meta-analysis. It has been shown, for instance, that there is a publication bias of studies dealing with the efficacy of ADMs during acute treatment (Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). For publication bias to explain our results, the likelihood of publication would have to be related to the perturbational effects of ADMs. This seems to us unlikely, but we cannot rule out this possibility.

Other limitations of this meta-analysis highlight difficulties with the ADM literature on which it is based. To address the question of how ADM discontinuation affects relapse rates, we were forced to rely on between-study relapse rates that may be biased by a number of other between-study differences, such as how relapse is defined. Prior meta-analyses have not dealt directly with this issue, despite evidence that definitional criteria affect relapse rates (Keller et al., 1998; Montgomery et al., 1993a). We constructed a stringency variable that measured the number of assessment hurdles that had to be passed before an increase in symptoms was deemed to be a relapse. As expected, this variable was a significant negative predictor of the relapse rate, and it generally improved the explanatory power of other variables in our analyses (results not shown), suggesting that the failure to take this variable into account can obscure findings. Nevertheless, our findings are necessarily correlational.

Is behavioral depression in rodents homologous to clinical depression in humans?

We could not use data on how ADMs perturb monoamine levels in humans. Such data do not exist because they require highly invasive techniques. Consequently, we used evidence on the perturbational effects in rat mPFC, which has been found to play a special role in processing

information about stressors and triggering depressive symptoms in response to repeated, uncontrollable shock (Amat et al., 2005). ADMs have dramatically different effects on monoamine levels in different brain regions (Dawson & Li, 2003; Valentini, Frau, & Di Chiara, 2004; Valentini, Cacciapaglia, Frau, & Di Chiara, 2005), so the gambit was that the perturbational effects in the rodent mPFC would predict the risk of relapse after ADM discontinuation in humans. This need not have been true.

Indeed, there are ongoing debates about whether behavioral measures of depression in rodents are good models of human depression (Anisman & Matheson, 2005; Kalueff, Wheaton, & Murphy, 2007; Nestler et al., 2002). These debates are, at least implicitly, about whether rodent models are homologous to depression in humans. Consequently, arguments tend to focus on whether the models induce behavioral symptoms in rodents that map onto depressive symptoms in humans, and whether the symptoms are alleviated by ADM treatment.

Our results show that the degree to which an ADM perturbs monoamines in the mPFC predicts the risk of depressive relapse in humans after discontinuation of the ADM. In other words, the region that predicts behavioral depression in rats also predicts depression in humans, which provides further evidence that rodent and human depression are homologous. Moreover, these results suggest that the rodent mPFC may be homologous to a region in the human brain that plays a similar role in clinical depression. One possible candidate is the VLPFC, of which the mPFC has been argued to be a structural and functional homologue (Kesner, 2000). The VLPFC has been implicated in clinical and subclinical depression and may play an important role in depressive rumination (Andrews et al., 2009; Drevets, 1998).

Are the symptoms currently used to diagnose MDD better characterized by disorder or adaptationist hypotheses?

Our results are also relevant to debates about whether the symptoms used to diagnose MDD are better characterized by disorder or adaptationist hypotheses. Of course, we cannot definitively answer this question. Our results are most relevant to claims that depressive episodes that meet diagnostic criteria for MDD are monoaminergic disorders.

If every disorder is to be understood as involving a malfunction in some adaptation (Wakefield, 1992), then mapping out the evolved structure and operation of adaptations can facilitate the identification of disorder by revealing the precise points where malfunction can occur. As discussed above, homeostatic mechanisms have sensor and feedback components, and some also have components for altering the equilibrium level of the parameter. To produce oppositional tolerance, the sensor component must be able to discern perturbations from equilibrium so that the feedback component can produce an oppositional force proportional to the degree of perturbation.

Our results support the conclusion that prolonged ADM use triggers oppositional tolerance in patients meeting diagnostic criteria for MDD. As predicted by an oppositional tolerance model, the risk of relapse was higher after ADM discontinuation than the unmedicated risk of relapse. Also, the risk of relapse after ADM discontinuation was proportional to the perturbational effect of the ADM on rodent mPFC. This result is analogous to the oppositional

force produced by a spring, which is proportional to the deviation from the equilibrium position. Our results therefore provide no evidence of malfunction in either the sensor or feedback components of monoaminergic homeostatic mechanisms in patients with episodes that satisfy current criteria for MDD.

However, it is possible that there could be some malfunction in the component that alters equilibrium monoamine levels. Demonstrating malfunction in this component requires more than merely showing that the equilibrium point is altered, since that is the function of this component. In other words, the claim that depression is a disorder in which monoamine levels are too high or too low is not simply supported by evidence that monoamine levels are altered since this could merely be the consequence of adaptive changes in the equilibrium levels in response to stressors. Undoubtedly, the equilibrium altering component must malfunction at some rate, but it is not clear that it is malfunctioning as frequently as current diagnostic criteria suggest. Understanding when it is malfunctioning will require greater research into the structure and operation of this component in response to stress. In any event, our results provide no positive evidence of malfunction in the homeostatic mechanisms regulating monoamine levels in people that meet diagnostic criteria for MDD.

Of course, our results do not speak to other possible malfunctions in patients who meet criteria for MDD. However, there is currently no evidence that the mechanisms regulating other neurochemicals are malfunctioning in patients diagnosed with MDD. The conceptual basis for considering an episode of depression to be a mental disorder is that it causes significant distress or impairment (American Psychiatric Association, 2000). However, it is clear that the body has evolved adaptations for causing significant pain and impairment.

For instance, organisms with infection can be incapacitated for days, weeks, or months, yet such incapacitation is usually considered to be an adaptive response to infection (Dantzer, 2001). Since mounting an effective immune response requires massive amounts of energy (Lochmiller & Deerenberg, 2000; Wolowczuk et al., 2008), social, sexual, locomotor, or cognitive activity could draw on limited energetic resources and interfere with the immune response. Consequently, the social, sexual, locomotor, and cognitive incapacity exhibited by sick organisms reflects an adaptive downregulation of systems that could otherwise interfere with mounting an effective immune response. Consistent with this, there is growing evidence that pharmacological disruption of fever, which is the best studied sickness behavior, prolongs infection and, for serious infections, may lower survivorship (Brandts, Ndjave, Graninger, & Kremsner, 1997; Hasday, Fairchild, & Shanholtz, 2000; Schulman et al., 2005).

In short, we found no positive evidence to support, and some positive evidence to contradict, the claim that most patients diagnosed with MDD have a monoaminergic disorder. Nor is there any evidence that the current diagnostic reliance on distress and impairment accurately identifies depressive disorder. Consequently, our results are just as consistent with adaptationist hypotheses, although they do not speak to the issue of what function depression may have evolved to serve.

Clinical implications

Our results have several important clinical implications.

Modest efficacy of ADMs during acute therapy

Hypotheses that depression is caused by a dysregulation in monoamine levels were developed based on drugs that lower symptoms and had monoaminergic properties, such as blockade of the serotonin transporter or inhibition of the MAO enzymes (Valenstein, 1998). However, these drugs also have limited efficacy during acute treatment (Fournier et al., 2010; Kirsch et al., 2008), which is one reason why researchers are investigating the role of other neurochemicals in depression (Krishnan et al., 2008). However, even if monoamines are the neurochemical cause of depression, the symptom-reducing effects of ADMs would be limited by the development of oppositional tolerance, which may explain why ADMs have limited efficacy.

Maintenance therapy

It is commonly thought that ADM treatment should continue until the index episode resolves, else relapse will recur. For this reason, maintenance ADM therapy is often recommended for 4-12 months or more after the acute management of the index episode (Geddes et al., 2003). Nevertheless, there are troubling empirical problems with these guidelines. For instance, in naturalistic studies, unmedicated patients have much shorter episodes, and better long-term prospects, than medicated patients (Coryell et al., 1995; Goldberg, Privett, Ustun, Simon, & Linden, 1998; Posternak et al., 2006). Several of these studies have found that the average duration of an untreated episode of major depression is 12-13 weeks (Coryell et al., 1995; Posternak et al., 2006). Since acute ADM management of major depression minimally requires several weeks to reduce symptoms, the duration of untreated episodes is much shorter than the recommended duration of ADM therapy. This suggests that ADM therapy may delay resolution of depressive episodes.

Current maintenance therapy guidelines are based primarily on prior meta-analyses that have found that the relapse rates in the Drug-Drug arms of ADM discontinuation studies are consistently lower than in the Drug-Placebo arms (Geddes et al., 2003; Glue et al., 2010; Kaymaz et al., 2008; Viguera et al., 1998). This is often interpreted as evidence that ADM therapy prevents depressive relapse. However, our results suggest that oppositional tolerance to the ADM contributes to the high risk of relapse in the Drug-Placebo arms of these studies, which undermines the rationale for maintenance therapy. Moreover, if continuous ADM therapy were needed until the index episode resolved, then ADM discontinuation studies with longer periods of continuous treatment should have lower relapse rates. This prediction has not been supported in any prior meta-analysis of ADM discontinuation studies. We also did not find treatment duration to have a protective effect on the risk of relapse. Rather, we found a non-significant trend for longer periods of continuous ADM treatment to be associated with a greater risk of relapse. Maintenance therapy guidelines should be re-examined.

Dependency on ADMs

Drugs that promote the risk of relapse or withdrawal upon discontinuation can cause dependence on the drug to prevent the return of symptoms (Chouinard, 2004). Consequently,

such drugs must be managed carefully and patients must provide informed consent for their use (Bursztajn & Brodsky, 1998). ADMs are sometimes prescribed to people with alcohol or illicit drug dependencies (Petrakis, Leslie, & Rosenheck, 2003), because the use of such substances to medicate feelings of anxiety and depression is thought to play a role in the dependency (Tomlinson, Tate, Anderson, McCarthy, & Brown, 2006). Ironically, the use of ADMs to help people wean off such substances might merely replace one dependency with another.

Treating depression with multiple psychotropic drugs

Since many patients on antidepressants alone do not achieve full remission (Rush et al., 2006), possibly due to oppositional tolerance, atypical antipsychotic drugs and other agents are increasingly prescribed to enhance the efficacy of ADMs. Our results suggest that the concurrent use of multiple drugs could cause greater monoaminergic perturbations, possibly further increasing the risk of relapse after they are discontinued.

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Appendix A: Studies that met inclusion criteria

Sample	Age	Sex (%)	Diagnosis	Diagnostic Criteria	Treatment resistant patients?	Min. # Prior Episodes	Criteria for Defining Relapse	Stringency
Anton et al. (1994)	NR	NR	MDD	DSM-III-R	No	0	Clinical judgment	1
Bremner & Smith (1996)	NR	75	MDD	DSM-III	No	0	HRSD>16	1
Claghorn & Feighner (1993)	41	28	MDD	DSM-III	No	0	HRSD>17	1
Detke et al. (2004)	44	74	MDD	RDC	No	0	HRSD within 30% of entry score before medication	1
Entsuah et al. (1996)	40	71	MDD	DSM-III-R	No	0	CGIS>3 for 2 weeks	2
Montgomery et al. (1993)	44	65	MDD	DSM-III-R	Yes	0	MADRS>21	1
Montgomery et al. (1998)	42	58	MDD	DSM-III	No	0	HRSD>15	1
Hochstrasser et al. (2001)	42	75	MDD	DSM-IV	Yes	2	MADRS>21+confirm in 3-7 days	2
Klysner et al. (2002)	75	72	MDD	DSM-IV	No	0	MADRS>21+confirm in 3-7 dyas	2
Montgomery et al. (1993)	44	65	MDD	DSM-III-R	Yes	0	MADRS>21	1
Robert et al. (1995)	47	69	MDD	DSM-III-R	No	0	MADRS>24+clinical judgment	2
Gorwood et al. (2007)	72	79	MDD	DSM-IV	No	0	MADRS>21 or lack of efficacy	1
Terra & Montgomery (1998)	45	78	MDD	DSM-III-R	No	2	(Clinical judgment + 5 DSM-III-R symptoms)+confirm 8 days later	4
Emslie et al. (2008)	12	36	MDD	CDRS-R	No	0	(CDRS-R40+worsening of symptoms for 2 weeks) or clinical judgment	1
Gilaberte et al. (2001)	44	77	MDD	DSM-III-R	No	1	DSM-III+((HRSD>17/CGIS>3) for 2 weeks)	3
McGrath et al. (2006)	38	55	MDD	DSM-IV	No	0	CGII>2 for 2 weeks	2
Montgomery et al. (1988)	NR	NR	MDD	DSM-III	No	1	HRSD>18	1
Reimherr et al. (1998)	41	77	MDD	DSM-III-R	No	0	(DSMIIIR for 2 weeks) or (HRSD>13 for 3 weeks)	2
Schmidt et al. (2000)	42	64	MDD	DSM-IV	No	0	DSMIV+(CGIS>3 for 2 weeks)	3
Dobson et al. (2008)	39	78	MDD	DSM-IV	No	0	(HRSD>13 or PSR>4) for 2 weeks	2
Montgomery & Dunbar (1993)	48	78	MDD	DSM-III-R (HRSD18)	No	2	CGIS>3 or DSM-III-R (without 2 week duration) or clinical judgment or 2 point increase in CGIS score since prior assessment or depressive symptoms for longer than 7 days	1
Cheung et al. (2008)	16	78	MDD	SADS	No	0	Clinical judgment	1
Doogan & Caillard (1992)	51	69	MDD	RDC	No	0	CGIS>3	1
Kamijima et al (2006)	38	63	MDD	DSM-IV	No	0	(HRSD>14+CGII>3) for 2 weeks	4
Keller et al. (1998)	42	69	MDD	DSM-III-R	Yes	0	((DSM-III for 3 weeks+CGIS>3 + CGII>2 +HRSD (4 points greater than	11

							maintenance score)), each confirmed again 1 week later) + confirmed by PI	
Lustman et al. (2006)	55	62	MDD	DSM-IV	No	0	(BDI>9 for 2 weeks or BDI>15)+DSM-IV	2
Wilson et al. (2003)	77	75	MDD	DSM-III-R	No	0	DSM-III-R+HRSD>12	2
Perahia et al. (2006)	45	78	MDD	DSM-IV	No	1	CGIS>3+(MINI for 2 weeks)	3
Perahia et al. (2009)	48	75	MDD	DSM-IV	No	2	(DSMIV+CGIS>3) for 2 weeks	4
Rickels et al. (2010)	43	68	MDD	DSM-IV	No	0	HRSD>15 or CGII>5	1
Rouillon et al. (2000)	45	68	MDD	DSM-III-R	Yes	1	DSM-III-R+HRSD>17+ need to treat	3
Kocsis et al. (2007)	43	67	MDD	DSM-IV	No	2	(HRSD>12 + HRSD score > than 50% of baseline score) for 2 visits + DSM-IV by senior investigator	4
Montgomery et al. (2004)	44	67	MDD	DSM-III-R	No	1	CGIS>3	1
Simon et al. (2004)	41	62	MDD	DSM-IV	No	0	(DSMIV+CGIS>3) or (CGIS>3 for 2 weeks)	2
Coppen et al. (1978)	52	81	Dep	MRC	Yes	0	Severe enough to be admitted to hospital	1
Klerman et al. (1974)	38	100	Dep	DSM-II	No	0	Clinical judgment	1
Stein et al. (1980)	42	65	MDD	Feighner and DSM-III	No	0	Worsening of symptoms for 3 weeks	3
Van Praag & De Haan (1980)	44	65	Dep	RDC	Yes	3	CGII>2 or HRSD>20	1
Kocsis et al. (1996)	37	57	MDD	DSM-III-R	Yes	0	(HRSD>12 for 3 out of 4 weeks) or (HRSD>12 for 1 week + urgent need for alternative treatment)	2
Stewart et al. (1997)	39	57	Mixed	DSM-III	Yes	0	CGII>2 for 2 weeks	2
Alexopoulos et al. (2000)	73	63	MDD	DSM-IV	No	0	RDC+DSM-IV+HRSD>16	3
Georgotas et al. (1989)	66	59	MDD	RDC	No	0	RDC+HRSD>16	2
Reynolds et al. (1999)	68	75	MDD	SADS	No	2	RDC+confirmed by senior psychiatrist	2
Davidson & Raft (1984)	NR	88	UPD	Feighner	No	0	Clinical judgment or patient request or HRSD>20	1
Georgotas et al. (1989)	64	50	MDD	RDC	No	0	RDC+HRSD>16	2
Harrison et al. (1986)	NR	83	MDD	DSM-III	Yes	0	CGII>2 for 2 weeks	2
Robinson et al. (1991)	43	81	MDD	DSM-III	No	1	(Depressive syndrome+confirmed by second therapist) for 2 weeks	4
Stewart et al. (1997)	39	57	Mixed	DSM-III	Yes	0	CGII>2 for 2 weeks	2
Amsterdam et al. (2006)	43	69	MDD	DSM-IV	No	0	(HRSD>13+CGIS>2+CGI score must have increased 2 points from baseline score+DSM-IV) for 2 weeks	8

Supplementary Material: Studies that met inclusion criteria (continued)

Study	ADM	Class	Treatment	Risk	# Relapse	N	Relapse	SE

			Duration (months)	Dropout rate	Period (months)			rate	
Anton et al. (1994)	Placebo	PBO	1.63	0.6979	12.00	22	71	0.3099	0.0549
Bremner & Smith (1996)	Placebo	PBO	1.40	NR	4.67	6	26	0.2308	0.0826
Claghorn & Feighner (1993)	Placebo	PBO	1.40	0.8083	12.00	8	46	0.1739	0.0559
Detke et al. (2004)	Placebo	PBO	1.87	0.3763	6.07	17	58	0.2931	0.0598
Entsuah et al. (1996)	Placebo	PBO	1.40	NR	12.00	26	119	0.2185	0.0379
Montgomery et al. (1993)	Placebo	PBO	6.00	0.5925	5.60	16	60	0.2667	0.0571
Montgomery et al. (1998)	Placebo	PBO	1.40	0.7047	4.67	13	57	0.2281	0.0556
Hochstrasser et al. (2001)	Citalopram	SSRI	5.48	0.3817	11.20	62	132	0.4697	0.0434
Klysner et al. (2002)	Citalopram	SSRI	5.60	0.4739	11.20	41	61	0.6721	0.0601
Montgomery et al. (1993)	Citalopram	SSRI	1.40	0.5925	5.60	14	42	0.3333	0.0727
Robert et al. (1995)	Citalopram	SSRI	1.87	0.4220	5.60	20	74	0.2703	0.0516
Gorwood et al. (2007)	Escitalopram	SSRI	2.80	0.2469	5.60	50	153	0.3268	0.0379
Terra & Montgomery (1998)	Fluvoxamine	SSRI	5.60	0.5321	12.00	32	94	0.3404	0.0489
Emslie et al. (2008)	Fluoxetine	SSRI	2.80	0.3964	5.60	36	52	0.6923	0.0640
Gilaberte et al. (2001)	Fluoxetine	SSRI	7.47	0.4466	11.20	28	70	0.4000	0.0586
McGrath et al. (2006)	Fluoxetine	SSRI	2.80	0.5404	12.13	94	131	0.7176	0.0393
Montgomery et al. (1988)	Fluoxetine	SSRI	5.60	0.5175	12.00	54	94	0.5745	0.0510
Reimherr et al. (1998)	Fluoxetine	SSRI	2.80	0.5292	2.80	46	95	0.4842	0.0513
Schmidt et al. (2000)	Fluoxetine	SSRI	3.03	0.4624	5.83	61	122	0.5000	0.0453
Dobson et al. (2008)	Paroxetine	SSRI	3.73	0.5100	12.00	12	21	0.5714	0.1080
Montgomery & Dunbar (1993)	Paroxetine	SSRI	1.87	0.2151	12.00	29	67	0.4328	0.0605
Cheung et al. (2008)	Sertraline	SSRI	2.80	0.7634	5.60	6	9	0.6667	0.1571
Doogan & Caillard (1992)	Sertraline	SSRI	1.87	0.6039	12.00	48	110	0.4364	0.0473
Kamijima et al (2006)	Sertraline	SSRI	1.87	0.3490	3.73	23	118	0.1949	0.0365
Keller et al. (1998)	Sertraline	SSRI	6.80	0.6221	17.73	19	84	0.2262	0.0456
Lustman et al. (2006)	Sertraline	SSRI	3.73	0.5670	12.13	38	73	0.5205	0.0585
Wilson et al. (2003)	Sertraline	SSRI	6.07	0.5551	23.33	30	57	0.5263	0.0661
Perahia et al. (2006)	Duloxetine	SNRI	2.80	0.4784	6.07	59	142	0.4155	0.0414
Perahia et al. (2009)	Duloxetine	SNRI	7.93	0.4397	24.00	47	142	0.3310	0.0395
Rickels et al. (2010)	Desvenlafaxine	SNRI	2.80	0.3687	5.60	90	185	0.4865	0.0367
Rouillon et al. (2000)	Milnacipran	SNRI	6.00	0.5720	12.00	26	110	0.2364	0.0405
Kocsis et al. (2007)	Venlafaxine	SNRI	8.33	0.5698	12.00	54	129	0.4186	0.0434
Montgomery et al. (2004)	Venlafaxine	SNRI	6.00	0.5253	12.00	64	116	0.5517	0.0462
Simon et al. (2004)	Venlafaxine	SNRI	1.87	0.3510	5.63	64	138	0.4638	0.0425
Coppen et al. (1978)	Amitriptyline	TCA	2.33	NR	10.00	5	16	0.3125	0.1159
Klerman et al. (1974)	Amitriptyline	TCA	1.17	0.4604	8.00	7	25	0.2800	0.0898
Stein et al. (1980)	Amitriptyline	TCA	1.87	0.5565	6.00	16	23	0.6957	0.0959
Van Praag & De Haan (1980)	Clomipramine	TCA	4.43	NR	12.00	8	10	0.8000	0.1265

Kocsis et al. (1996)	Desipramine	TCA	6.53	0.4884	24.00	12	25	0.4800	0.0999
Stewart et al. (1997)	Imipramine	TCA	8.87	NR	6.00	7	15	0.4667	0.1288
Alexopoulos et al. (2000)	Nortriptyline	TCA	3.73	0.5700	24.00	11	21	0.5238	0.1090
Georgotas et al. (1989)	Nortriptyline	TCA	5.83	NR	12.00	7	14	0.5000	0.1336
Reynolds et al. (1999)	Nortriptyline	TCA	6.93	0.3369	36.00	26	29	0.8966	0.0566
Davidson & Raft (1984)	Phenelzine	MAOI	1.75	NR	5.00	8	8	1.0000	0.0764
Georgotas et al. (1989)	Phenelzine	MAOI	5.83	NR	12.00	8	9	0.8889	0.1048
Harrison et al. (1986)	Phenelzine	MAOI	4.69	NR	6.00	7	7	1.0000	0.0856
Robinson et al. (1991)	Phenelzine	MAOI	5.04	0.4659	24.00	13	16	0.8125	0.0976
Stewart et al. (1997)	Phenelzine	MAOI	7.47	NR	6.00	13	15	0.8667	0.0878
Amsterdam et al. (2006)	Selegiline	MAOI	2.33	0.5230	12.00	50	163	0.3067	0.0361

Abbreviations: BDI (Beck Depression Inventory); CDRS-R (Children's Depression Rating Scale-Revised); CGI-I (Clinical Global Impression-Improvement scale); CGI-S (Clinical Global Impression-Severity scale); Dep (primary depressive illness); DSM (Diagnostic and Statistical Manual of Mental Disorders); HRSD (Hamilton Research Scale for Depression); MADRS (Montgomery-Asberg Depression Research Scale); MRC (Medical Research Council criteria); NR (not reported); RDC (Research Diagnostic Criteria); SADS (Schedule for Affective Disorders and Schizophrenia for Children); UPD (unipolar depression).

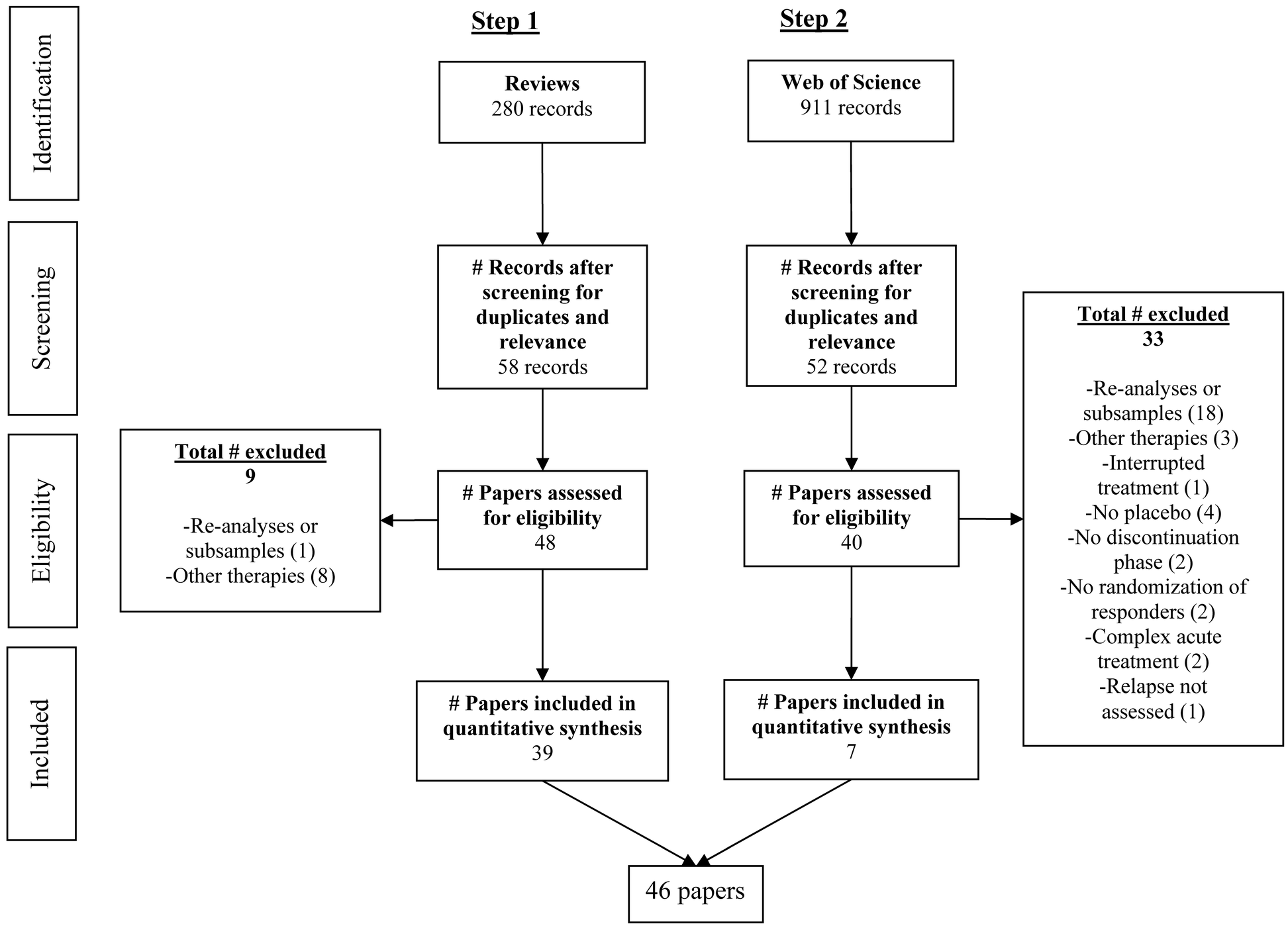
Figure legends

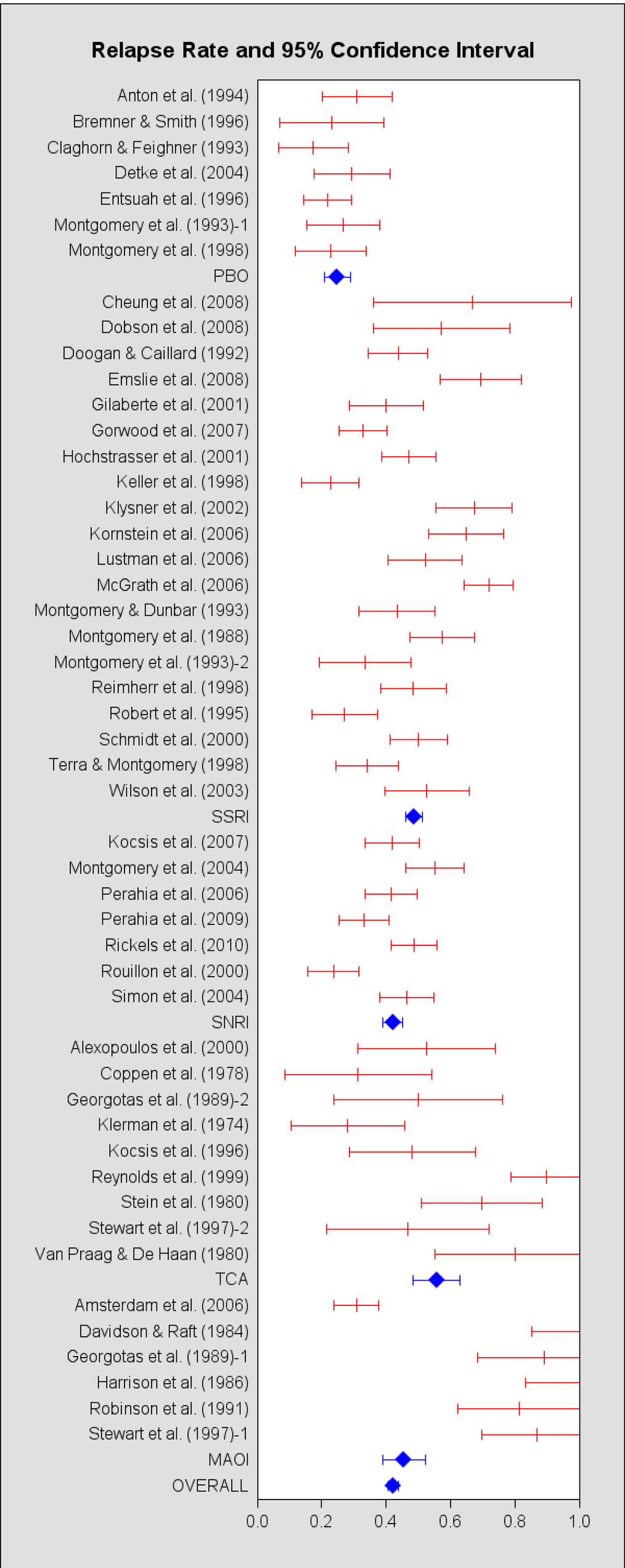
Figure 1. Flow diagram of the search strategy.

Figure 2. Forest plot of the relapse rate and 95% confidence interval for each study meeting inclulsion criteria.

Figure 3. Unadjusted proportions (with standard error bars) of patients with a relapse after discontinuation (to placebo) (y-axis) as a function of the stringency of the definition of relapse (x-axis) for each ADM class.

Figure 1. Flow diagram.




Relapse Rate and 95% Confidence Interval
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Bremner & Smith (1996)
Claghorn & Feighner (1993)
Detke et al. (2004)
Entsuah et al. (1996)
Montgomery et al. (1993)-1
Montgomery et al. (1998)
PBO
Cheung et al. (2008)
Dobson et al. (2008)
Doogan & Caillard (1992)
Emslie et al. (2008)
Gilaberte et al. (2001)
Gorwood et al. (2007)
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Kornstein et al. (2006)
Lustman et al. (2006)
McGrath et al. (2006)
Montgomery & Dunbar (1993)
Montgomery et al. (1988)
Montgomery et al. (1993)-2
Reimherr et al. (1998)
Robert et al. (1995)
Schmidt et al. (2000)
Terra & Montgomery (1998)
Wilson et al. (2003)
SSRI
Kocsis et al. (2007)
Montgomery et al. (2004)
Perahia et al. (2006)
Perahia et al. (2009)
Rickels et al. (2010)
Rouillon et al. (2000)
Simon et al. (2004)
SNRI
Alexopoulos et al. (2000)
Coppen et al. (1978)
Georgotas et al. (1989)-2
Klerman et al. (1974)
Kocsis et al. (1996)
Reynolds et al. (1999)
Stein et al. (1980)
Stewart et al. (1997)-2
Van Praag & De Haan (1980)
TCA
Amsterdam et al. (2006)
Davidson & Raft (1984)
Georgotas et al. (1989)-1
Harrison et al. (1986)
Robinson et al. (1991)
Stewart et al. (1997)-1
MAOI
OVERALL
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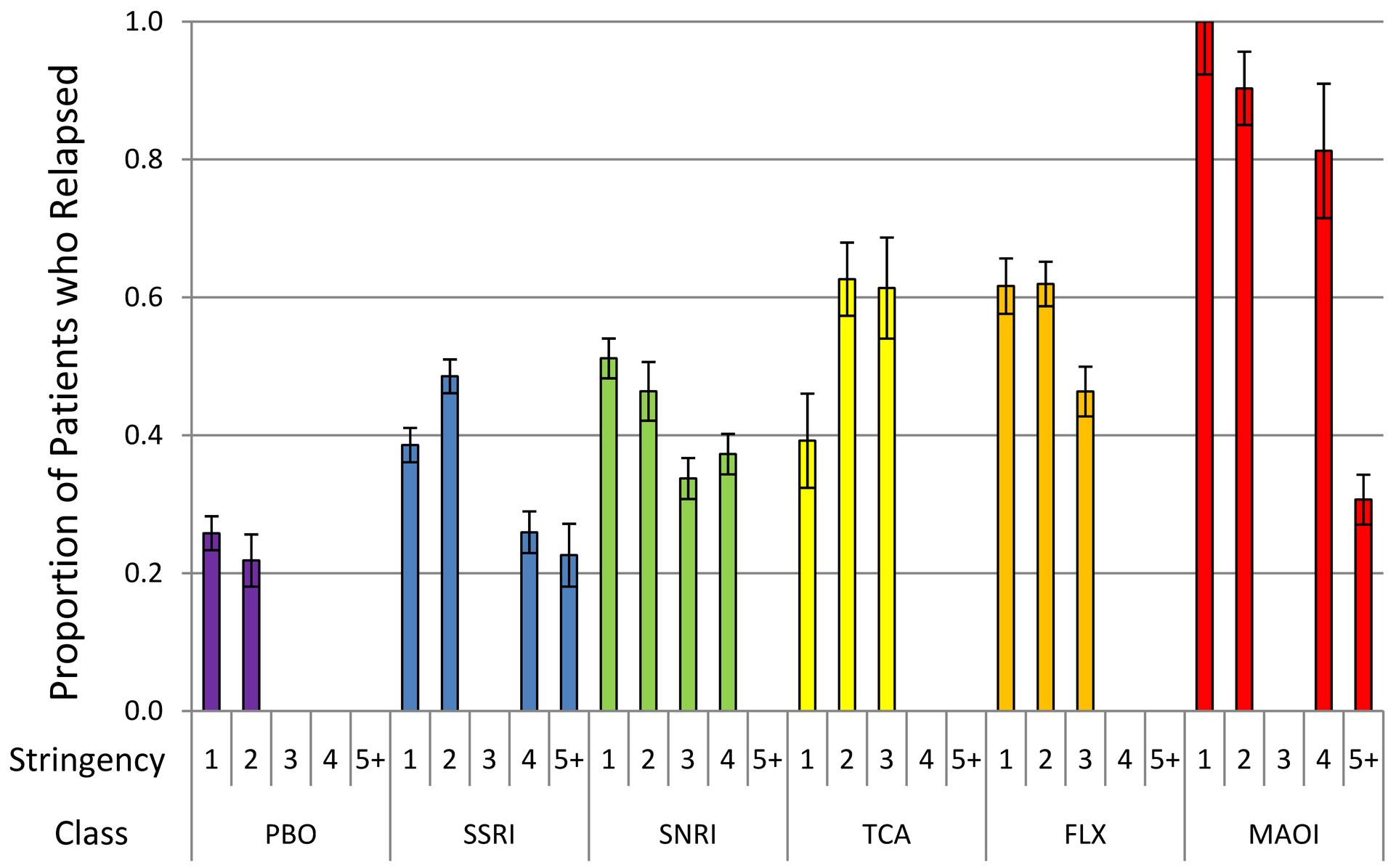
0.2
0.4
0.6
0.8
1.0


Proportion of Patients who Relapsed
1.0
0.8
0.6
0.4
0.2
0.0
Stringency
1 2 3 4 5+ 1 2 3 4 5+ 1 2 3 4 5+ 1 2 3 4 5+ 1 2 3 4 5+ 1 2 3 4 5+
Class
PBO
SSRI
SNRI
TCA
FLX
MAOI