

The other face of depression, reduced positive affect: the role of catecholamines in causation and cure

Journal of Psychopharmacology
00(0) (2006) 000–000
© 2006 British Association
for Psychopharmacology
ISSN 0269-8811
SAGE Publications Ltd,
London, Thousand Oaks,
CA and New Delhi
10.1177/0269881106069938

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Abstract

Despite significant advances in pharmacologic therapy of depression over the past two decades, a substantial proportion of patients fail to respond or experience only partial response to serotonin re-uptake inhibitor antidepressants, resulting in chronic functional impairment. There appears to be a pattern of symptoms that are inadequately addressed by serotonergic antidepressants – loss of pleasure, loss of interest, fatigue and loss of energy. These symptoms are key to the maintenance of drive and motivation. Although these symptoms are variously defined, they are consistent with the concept of 'decreased positive affect'. Positive affect subsumes a broad range of positive mood states, including feelings of happiness (joy), interest, energy, enthusiasm, alertness and self-confidence. Although preliminary, there is evidence to suggest that antidepressants that enhance noradrenergic and dopaminergic activity may afford a therapeutic advantage over serotonergic antidepressants in the treatment of symptoms associated with a reduction in positive affect. Dopaminergic and noradrenergic agents, including the dual acting

norepinephrine and dopamine re-uptake inhibitors, have demonstrated antidepressant activity in the absence of serotonergic function, showing similar efficacy to both tricyclic and serotonin re-uptake inhibitor antidepressants. Moreover, the norepinephrine and dopamine re-uptake inhibitor bupropion has been shown to significantly improve symptoms of energy, pleasure and interest in patients with depression with predominant baseline symptoms of decreased pleasure, interest and energy.

Focusing treatment on the predominant or driving symptomatology for an individual patient with major depression could potentially improve rates of response and remission.

Keywords

MeSH (max 10): major depressive disorder; catecholamines; dopamine; norepinephrine; bupropion; positive affect.

Introduction

Major depressive disorder (MDD) is one of the most common single mental disorders in Europe (13% lifetime and 4% 12-month prevalence rates) (Alonso *et al.*, 2004a, b). It is often a chronic, recurrent condition that severely impacts the quality of life of both the sufferer and their family and is associated with high levels of functional disability (Ormel *et al.*, 1999; Alonso *et al.*, 2004b). Moreover, individuals with depression are significantly higher

utilisers of healthcare resources compared with non-depressed individuals, with antidepressant non-responders being among the most resource intensive (Pearson *et al.*, 1999).

Research over the past 20 years has primarily focused on the role of serotonin (5-HT) in the pathophysiology and treatment of MDD. However, since the 1960s it has been recognized that norepinephrine (NE) and dopamine (DA) also play an integral part in the underlying pathophysiology of MDD, as well as a central role in the neurophysiology of a number of highly prevalent, chronic

and debilitating symptoms of depression (Schildkraut, 1965; Willner 1983a, b; 1995; Delgado, 2000, 2004).

Researchers have proposed the existence of two broad mood factors – positive and negative affect (Watson *et al.*, 1984; Watson and Tellegen, 1985; Watson and Clark 1988; Clark and Watson, 1991; Watson *et al.*, 1995a, b; Shelton and Tomarken, 2001) which are highly distinctive dimensions that are uncorrelated. Positive affect subsumes a broad range of positive mood states, including feelings of happiness (joy), interest, energy, enthusiasm, alertness and self-confidence. In contrast, negative affect is a general factor of subjective distress and subsumes a broad range of negative mood states, such as fear, anxiety, irritability, loneliness, guilt, disgust and hostility, and it is common to both mood and anxiety disorders (Clark and Watson, 1991). Patients with major depression commonly exhibit symptoms of loss of interest, loss of energy and loss of motivation, i.e. core symptoms of depression associated with ‘decreased positive affect’ (Watson and Clark, 1988; Clark and Watson, 1991). Symptoms of ‘decreased positive affect’ and loss of pleasure (anhedonia) are consistently correlated with depression (Watson and Clark, 1988; Watson *et al.*, 1995a, b). Loss of pleasure will therefore be included in the definition of ‘decreased positive affect’ described in this paper (Fig. 1). There is preliminary evidence to suggest that antidepressants that enhance noradrenergic and dopaminergic activity may afford a therapeutic advantage over serotonergic antidepressants in the treatment of these symptoms (Bremner *et al.*, 1984; Rampello *et al.*, 1991; Dalery *et al.*, 1997; Jouvent *et al.*, 1998; Jamerson *et al.*, 2003; Papakostas, 2006; Jefferson *et al.*, in press).

Fig. 1 is a hypothetical model which illustrates the differential actions of antidepressants on symptoms of positive and negative affect. Serotonergic antidepressants appear to be more effective in treating symptoms associated with negative affectivity such as fear, anxiety, and irritability (symptoms that are predominant in depression with co-morbid anxiety). Preliminary data suggest that antidepressants with dopaminergic and noradrenergic activity may

be more effective in treating depressive symptoms associated with the loss of positive affect.

In this article, we review the roles of NE, DA and 5-HT in the treatment of MDD overall and, in particular, focus on the symptoms of ‘decreased positive affect’ – loss of pleasure, loss of interest, fatigue or loss of energy and loss of motivation (Watson and Clark, 1988; Shelton and Tomarken, 2001).

Current unmet medical needs

The introduction of the SSRIs in the late 1980s with their improved safety profile and general ease of administration, facilitated the management of unipolar depression within a primary care environment. The SSRIs have since become established as first-line therapy for the treatment of major depression. However, a substantial proportion of patients fail to respond to SSRI therapy (28–55%), the onset of antidepressant efficacy is often delayed and many patients continue to experience residual symptoms and an incomplete response to therapy (Nierenberg *et al.*, 1999; Nierenberg and DeCocco, 2001; Peterson *et al.*, 2005; Trivedi *et al.*, 2006). Residual symptoms and partial response are accurate predictors of early relapse and recurrence of depression. Relapse rates are estimated to be between three to six times higher in patients with residual symptoms compared with those who experience full symptomatic remission (Thase *et al.*, 1992; Paykel *et al.*, 1995; Rush and Trivedi, 1995; Judd *et al.*, 1998; Lecrubier, 2002; Paykel, 2002). Subsyndromal depressive symptoms, that persist following resolution of the depressive episode or exist in the absence of a major depressive episode (MDE), are also associated with an increased risk of suicide or suicidal ideation, increased healthcare utilisation, and a greater reliance on disability benefits (Lecrubier, 2000). A long-term (8–10 years) naturalistic follow-up study of patients with severe recurrent depression who were in remission (defined as two consecutive months with symptoms below definite Research Diagnostic Criteria for major depression), showed that patients continued to experience low-grade chronic depressive symptoms that resulted in long-term social and occupational impairment (Kennedy and Paykel, 2004). It is estimated that only 25% to 50% of patients in clinical trials achieve full remission of their depressive symptoms (Rush and Trivedi, 1995; Thase *et al.*, 2001; Casacalenda *et al.*, 2002; Smith *et al.*, 2002); even after prolonged (more than 6 months) therapy (Nierenberg and DeCocco, 2001). Moreover, approximately 30% to 50% of those who remit will continue to experience depressive symptomatology (Fawcett, 1994; Bothwell and Scott, 1997; Nierenberg *et al.*, 1999).

There are a limited number of studies available systematically evaluating the presence and nature of residual symptoms following treatment with antidepressants or psychotherapy. However, published data suggest that residual symptoms typically include symptoms, such as sleep disturbances, diminished pleasure, loss of interest, fatigue or loss of energy and decreased motivation (Kopta *et al.*, 1994; Barkham *et al.*, 1996; Opdyke *et al.*, 1996–1997; Nierenberg *et al.*, 1999; Shelton and Tomarken, 2001). In an open-label study of 215 patients with major depression treated with

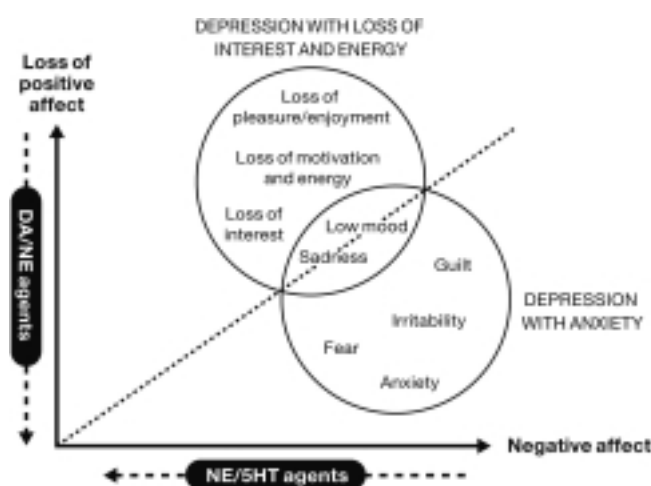


Figure 1 Hypothetical model showing differential actions of antidepressant agents on symptoms of positive and negative affect

20mg/day fluoxetine for 8 weeks, the most common residual symptoms in patients who achieved remission ($\text{HAM-D} \leq 7$) were sleep disturbances (44%), fatigue (38%) and diminished pleasure or interest (38%) (Nierenberg *et al.*, 1999).

Fatigue and loss of energy are the most common depressive symptoms reported in primary care and are risk factors for unrecognised depression (Tylee *et al.*, 1993; Suh and Gallo, 1997). The vast majority of patients who present with MDD in primary and secondary care, 73%–97%, complain of fatigue or loss of energy (Baker *et al.*, 1971; Tylee *et al.*, 1999; Demyttenaere *et al.*, 2004). Loss of pleasure and loss of interest are also commonly reported presenting symptoms (Maurice-Tison *et al.*, 1998; Gaynes *et al.*, 2005; Nelson *et al.*, 2005). Symptoms of fatigue or loss of energy and loss of interest appear to be more difficult to treat and respond more slowly to existing therapy, including psychotherapy (Kopka *et al.*, 1994; Opdyke *et al.*, 1996–1997; Boyer *et al.*, 2000; Demyttenaere *et al.*, 2004).

Baseline fatigue or loss of energy and loss of interest were shown to be the best predictors of failure to achieve remission with antidepressant therapy in a naturalistic study of 313 depressed patients followed over a 10-year period (Moos and Cronkite, 1999). In a further naturalistic study of depressed patients in primary care, loss of energy was found to correlate most strongly with an increased number of days in bed, days off work, reduced work productivity and diminished ability to function socially at baseline and at 3 months follow-up (Swindle *et al.*, 2001). An epidemiological survey in a representative sample of the 7076 individuals from the general population of the Netherlands (NEMESIS) also found that symptoms of loss of pleasure and loss of interest associated with depression were risk factors for poor clinical outcome at 1 year (Spijker *et al.*, 2001).

There appears to be a pattern of symptoms that are currently inadequately addressed by serotonergic antidepressants – loss of pleasure, loss of interest, fatigue and loss of energy – each of which contribute to the loss of drive and motivation. Although different classifications and descriptors exist, this group of symptoms are consistent with ‘decreased positive affect’ (Watson and Clark, 1988). There are data to suggest that symptoms of ‘decreased positive affect’ are associated with dysregulation of DA and NE neurotransmission (Gold and Chrousos, 1998; Schmidt *et al.*, 2001).

NE, DA and 5-HT in the treatment of MDD overall

Data from controlled comparative clinical trials suggest that antidepressants that enhance NE, DA and/or 5-HT activity have similar levels of overall efficacy in the treatment of MDD. Monoamine oxidase inhibitors (MAOIs) prevent the catabolism of NE, DA and 5-HT neurotransmitters and have been shown to be effective antidepressants. However, their use is limited due to the risk of serious and potentially lethal adverse events such as hypertensive crises and serotonin syndrome, and the requirement for strict dietary restrictions. As a result, MAOIs are rarely selected as first-line treatment for MDD.

NE-selective compounds have been shown to be effective antidepressants, e.g. the noradrenergic tricyclic antidepressant (TCA) desipramine. The selective NE re-uptake inhibitor (NRI) reboxetine has also demonstrated equivalent overall efficacy to the TCAs and SSRIs in the treatment of MDD (reviewed in Montgomery, 1997; Massana, 1998). Moreover, dual-acting antidepressants with a broader pharmacological profile, i.e., the SNRIs, venlafaxine, milnacipran and duloxetine, have shown similar rates of response to the SSRIs (Clerc *et al.*, 1994; Lopez-Ibor *et al.*, 1996; Entsuah *et al.*, 2001; Detke *et al.*, 2004). However, there are data to suggest that the SNRIs may be more effective than the SSRIs in the achievement of clinical remission (Lopez-Ibor *et al.*, 1996; Nemeroff *et al.*, 2002; Smith *et al.*, 2002; Thase, 2003). Preclinical data suggest that venlafaxine also prevents the re-uptake of DA, although to a lesser extent than 5-HT and NE (reviewed in Bourin, 1999). The inhibition of DA re-uptake is unlikely to be relevant at clinically approved doses.

More recently, interest has turned to the role of DA in depression. This is based on a wide body of preclinical data (reviewed in D’Aquila *et al.*, 2000; Willner, 2000), the postulation by Klein (1974) that loss of interest and pleasure (anhedonia) are the core symptoms of depression and that all other depressive symptoms are causally related, and clinical evidence identifying low concentrations of homovanillic acid (HVA, a metabolite of DA) in the cerebrospinal fluid (CSF) (for reviews see Willner, 1983a; Papakostas, 2006) and plasma of depressed patients (Lambert *et al.*, 2000). Furthermore, data from clinical studies have shown that DA agonists, such as bromocriptine, pramipexole and ropinirole, exhibit antidepressant properties (Sitland-Marken *et al.*, 1990; Corrigan *et al.*, 2000; Cassano *et al.*, 2005). Amineptine, a TCA-derivative that predominantly inhibits DA re-uptake and has minimal noradrenergic and serotonergic activity (Garattini and Mennini, 1989; Garattini, 1997) has also been shown to possess antidepressant activity (Boyer *et al.*, 1999). A number of studies have suggested that amineptine has similar efficacy to the TCAs, MAOIs and SSRIs (Macher and Mirabaud, 1992; Rampello *et al.*, 1995; Dalery *et al.*, 1997). However, amineptine is no longer available as a treatment for depression due to reports of an abuse potential. This has raised concerns about the potential reinforcing effects of agents that block dopamine transporters (DAT). Volkow and colleagues (1995, 1997, 1998) have demonstrated that, for these drugs to be reinforcing, they must block more than 50% of the DAT within a relatively short time period (<15 minutes from administration) and clear the brain rapidly to enable fast repeated administration.

The dual-acting NE and DA re-uptake inhibitor (NDRI) bupropion (Stahl *et al.*, 2004) has demonstrated similar efficacy to the SSRIs and TCAs in the treatment of MDD (Feighner *et al.*, 1986, 1991; Kiev *et al.*, 1994; Weisler *et al.*, 1994; Kavoussi *et al.*, 1997; Croft *et al.*, 1999; Weihs *et al.*, 2000). Bupropion exhibits a relatively low potency in blocking DAT (approximately 14–26%, Meyer *et al.*, 2002; Learned-Coughlin *et al.*, 2003; Árgyelán *et al.*, 2005) and the rate of occupancy is slow at therapeutic doses (150–300mg/day) (Learned-Coughlin *et al.*, 2003; Stahl *et al.*, 2004). It is therefore unlikely to exhibit a reinforcing effect.

Despite the fact that the majority of existing antidepressants appear to exhibit similar efficacy in the overall treatment of

depression, antidepressants with different profiles of action may more effectively target specific symptoms within the depressive syndrome (Stahl *et al.*, 2003). If this is the case, treatment could be more accurately focused on the predominant or driving symptomatology for an individual patient. This could potentially improve rates of response and remission.

Linking neurotransmitters, circuits and specific symptoms of depression

Recent advances in functional neuroimaging techniques, primarily Positron Emission Tomography (PET), have enabled researchers to identify consistent neuroanatomical correlates of MDD. Reduced cerebral blood flow (CBF) or glucose metabolism has been consistently observed in the prefrontal cortex, anterior cingulate cortex and the caudate nucleus. These changes all recover upon remission of MDD (reviewed in Videbech, 2000). However, reviews of the functional brain imaging literature note inconsistencies between studies that have led to speculation that clinical heterogeneity among MDD symptoms may account for variable imaging findings (for reviews see Kennedy *et al.*, 1997; Drevets *et al.*, 1998; Videbech 2000). A greater understanding of the neurotransmitters and brain circuits involved in specific symptoms of major depression may enable a more targeted approach to treatment.

Depressed mood and sadness

Depressed mood is widely recognised as one of the defining symptoms of major depression. Functional neuroimaging studies have most commonly associated depressed mood and sadness with abnormal neuronal activity in the medial prefrontal cortex, including the anterior cingulate and orbitofrontal cortex (Drevets, 1999; Mayberg *et al.*, 1999; Davidson *et al.*, 2002; Drevets *et al.*, 2002; Liotti *et al.*, 2002; Levesque *et al.*, 2003). These brain regions receive innervation from serotonergic (midbrain raphe), noradrenergic (locus coeruleus) and dopaminergic (ventral tegmental, VTA) pathways. Low levels of NE, 5-HT and DA may be associated with low mood, and antidepressants that enhance levels of these monoamine neurotransmitters have been shown to improve depressed mood and sadness (Zung *et al.*, 1983; Reimherr *et al.*, 1998; Davidson *et al.*, 2002; Davies *et al.*, 2003).

Diminished interest or pleasure

A high proportion of patients with MDD experience diminished interest or pleasure in their daily activities and things they would normally have enjoyed. Reduced dopaminergic activity has been linked to decreased incentive motivation (Salamone, 1996; Salamone *et al.*, 2003), anhedonia (loss of pleasure) (reviewed in: D'Aquila *et al.*, 2000; Delgado, 2000; Willner, 2000) and loss of interest (Wise, 1982; Willner, 1983a, b, c), whereas increased functional dopaminergic activity has been linked to positive affect (Depue *et al.*, 1994; Depue and Collins, 1999). The mesocorticolimbic dopaminergic pathway, in particular the nucleus accumbens,

is a key regulator of pleasure (reviewed in: Chau *et al.*, 2004). The ventral striatum (nucleus accumbens and olfactory tubercle) and prefrontal cortex are believed to be important regions involved in motivation and affect (Drevets, 2001). A dysfunction (e.g. hypo-function) of the mesocorticolimbic DA system – which innervates limbic structures, such as the nucleus accumbens, amygdala, ventral hippocampus and cortical areas such as the prefrontal cortex – may underlie the symptoms of loss of motivation, loss of interest and the inability to experience pleasure observed in MDD. Therefore, antidepressants that enhance dopamine release in the mesocorticolimbic regions may improve symptoms of loss of pleasure, interest and lack of motivation.

Fatigue and loss of energy

Symptoms of fatigue and loss of energy are poorly understood and their exact neurobiological basis has not been elucidated. Symptoms of fatigue and loss of energy can be physical or mental in nature. Hypothetically, brain areas controlling motor function may be involved in physical fatigue, e.g. the striatum (innervated by dopaminergic and serotonergic neurones) and cerebellum (innervated by noradrenergic neurones) (Stahl *et al.*, 2003). 5-HT inhibits DA release in the striatum. Mental fatigue and lack of mental energy may be related to other symptoms of depression, such as apathy (absence in feeling, emotion, interest or concern) and lack of motivation. Cortical brain regions, especially the dorsolateral prefrontal cortex (DLPFC), are more likely to be involved in mental fatigue (MacHale *et al.*, 2000). Antidepressants that increase NE and DA, or both, particularly in the pathways associated with physical and mental fatigue, may be preferable for patients with predominant symptoms of fatigue and loss of energy (Bodkin *et al.*, 1997; Stahl *et al.*, 2003; Demyttenaere *et al.*, 2004).

Anxiety

The neurocircuitry of fear appears to focus on the amygdala. The amygdala receives noradrenergic innervation from the locus coeruleus and serotonergic projections from the midbrain raphe nuclei. Davidson and colleagues (2002) have suggested that high levels of amygdala activation are associated with an increased prevalence of anxiety symptoms and dispositional negative affect. Electrical stimulation of the amygdala can evoke emotional experiences, especially fear and anxiety, and vivid recall of emotional life events (Gloor *et al.*, 1982; Brothers, 1995). Bremner and co-workers (1997) reported that antidepressant-medicated MDD subjects who relapsed in response to serotonin depletion had a higher amygdala metabolism prior to depletion than similar subjects who did not relapse, suggesting that abnormal amygdala activity may involve susceptibility to symptom recurrence, and episode severity. Antidepressants that target 5-HT and NE may be more appropriate for treating patients with depression with comorbid anxiety disorders.

Although not completely clear, the balance of evidence is that depressed positive affect (loss of pleasure, interest, energy and motivation) appears to be most closely related to dysfunctions in

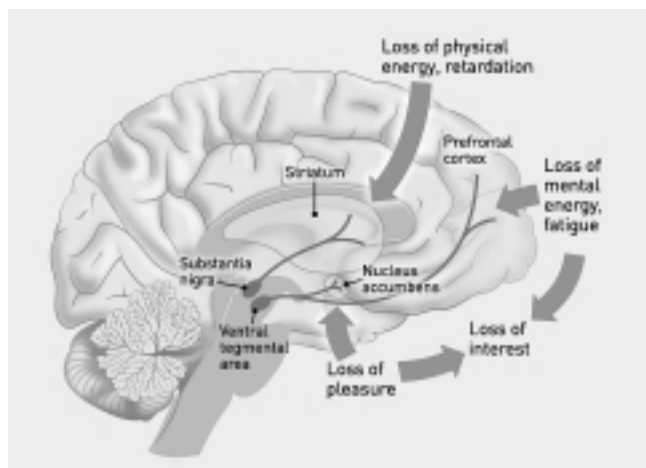


Figure 2 Schematic diagram of brain dopamine systems and possible sites of symptom generation

NE and DA circuits. Conversely, symptoms of negative affect appear to be most closely related to 5-HT and NE circuits. Fig. 2 shows a schema for understanding the role of dopamine in these functions.

What is the clinical evidence?

Limited clinical data exist to support this hypothesis. This is perhaps unsurprising given the fact that the majority of standard anxiety and depression rating scales are heavily weighted towards symptoms of general distress or negative affect and cannot discriminate between dimensions of mood (Clark and Watson, 1991; Shelton and Tomarken, 2001). Evidence of symptomatic improvement in scales such as HAM-D and MADRS primarily reflect a reduction in symptoms of general distress that are common to both anxiety and depressive disorders.

Loss of pleasure (anhedonia)

A few studies have compared the efficacy of different classes of antidepressants with respect to the treatment of loss of pleasure. In one double-blind trial, treatment of the monoamine oxidase A (MAO-A) selective inhibitor moclobemide (450 mg/day) resulted in an earlier improvement in anhedonia and blunted affect in patients with MDD than the predominantly serotonergic TCA clomipramine (Jouvent *et al.*, 1998). The authors hypothesized that the early efficacy of moclobemide on anhedonia, blunted affect and retardation may be related to its ability to increase synaptic levels of DA. Massana (1998) summarized the results of two 8-week clinical trials comparing the NRI reboxetine (8–10 mg/day) to fluoxetine (20–40 mg/day) in 549 patients with MDD. Reboxetine was associated with a greater improvement in social functioning, especially in terms of motivation towards action and negative self-perception than fluoxetine. Furthermore,

the noradrenergic TCA desipramine (mean maximum daily dose=238 mg) has been shown to be effective in treating more than 80% of depressed patients ($n=33$ total) with pervasive anhedonia in an open-label trial (Stewart *et al.*, 1980).

There is evidence to suggest that symptoms of anhedonia/loss of pleasure may respond more slowly, compared to other MDD symptom clusters, in patients treated with SSRIs. Boyer and co-workers (2000) treated 140 outpatients with MDD with sertraline (50–150 mg/day) in an open-label clinical trial and found that improvement in the anxiety cluster was greatest during days 0–7, whereas most improvement was observed in the depression cluster during days 7–21. The greatest improvement in the hedonic cluster did not occur until days 21–56. It should be noted that sertraline has a relatively high affinity for the DA re-uptake transporter (DAT) (K_i 230 nM) (Goodnick and Goldstein, 1998).

Loss of interest and motivation

The dopaminergic and noradrenergic agent nomifensine has been found to be equally effective in the treatment of depression to the TCA imipramine, but superior to imipramine with respect to interest in work and activities (Bremner *et al.*, 1984). This finding is supported by anecdotal data based on individual case studies, which suggest that dopamine agonists and the NDRI bupropion may be effective in treating symptoms of apathy (defined as lack of emotion or interest and decreased motivation) (Barrett, 1991; Marin *et al.*, 1995; Corcoran *et al.*, 2004).

In contrast, a number of case-series report the emergence of apathy during treatment with various SSRIs. SSRIs have been shown to decrease both NE and DA neurotransmission acutely (Prisco and Esposito, 1995), probably via stimulation of 5-HT_{2A} and 5-HT_{2C} receptors (Gobert *et al.*, 2000; Di Matteo *et al.*, 2001). This may explain the symptoms of apathy and listlessness that are reported by some patients, especially in early treatment. Hoehn-Saric and co-workers (1990) reported apathy, indifference and loss of initiative in panic disorder and depressed patients receiving SSRIs. The same group (Hoehn-Saric *et al.*, 1991) also reported the emergence of apathy accompanied by decreased frontal-lobe blood flow in a patient with obsessive compulsive disorder (OCD) treated with high doses of fluoxetine. These symptoms disappeared within 4 weeks of fluoxetine discontinuation. Garland and Baerg (2001) described the emergence of amotivation and apathy in four children and one adolescent with a variety of psychiatric diagnoses, treated with SSRIs, that was reversible with SSRI dose-reduction or discontinuation. Finally, Opbroek and colleagues (2002) studied 15 outpatients maintained on SSRIs who reported sexual dysfunction and found that 80% of these patients also described significant blunting of several emotions including the ability to cry, caring less about others' feelings, decreased creativity, not being easily surprised, and decreased expression of their feelings.

Fatigue and loss of energy

A meta-analysis of controlled trials comparing MAOIs and TCAs conducted by Thase and colleagues (1995) suggested that the

MAOIs may preferentially treat TCA-resistant depression, especially in patients with features such as fatigue, volition inhibition, motor retardation and hypersomnia. This may be a function of the ability of MAOIs to increase synaptic levels of DA in addition to 5-HT and NE. The MAOIs also seem to be effective in the treatment of fatigue associated with fibromyalgia (FM) or chronic fatigue syndrome (CFS) (Natelson *et al.*, 1996; White and Cleary, 1997; Hannonen *et al.*, 1998; Natelson *et al.*, 1998; Hickie *et al.*, 2000).

The NDRI bupropion may improve symptoms of loss of energy (Bodkin *et al.*, 1997; Shelton and Tomarken, 2001; Tomarken *et al.*, 2004). Bodkin and colleagues (1997) found that five out of six patients receiving bupropion (up to 300mg/day) reported a subjective improvement in energy. The SSRIs significantly reduced panic and anxiety symptoms in 18 out of 20 patients with depression but did not improve energy. Indeed, ten of the 21 patients reported a subjective decrease in energy during SSRI therapy.

A recent analysis of symptom clusters from the 31-item HAMD scale by Jamerson and colleagues (2003) for 910 outpatients with MDD, found that the sustained release (SR) formulation of bupropion (300–400mg/day) was associated with a significantly greater reduction on certain symptom domains, including retardation (retardation, psychic retardation, motor retardation and loss of libido items) and fatigue and interest (oversleeping, hypersomnia, napping, work and interest and anergia items), compared with placebo.

There are also reports suggesting the potential efficacy of bupropion for SSRI-induced fatigue (Green, 1997) and in SSRI-resistant chronic-fatigue syndrome (Goodnick *et al.*, 1992). In addition, an open-label study of bupropion in 20 cancer patients with fatigue, or depression with marked fatigue, reported improvements in symptoms of fatigue within 2–4 weeks of the onset of therapy (Cullum *et al.*, 2004). Retrospective analyses of data pooled from double-blind, placebo-controlled studies have also shown that fewer bupropion- than SSRI-treated MDD patients complain of fatigue (Trivedi *et al.*, 2001; Fava *et al.*, 2005; Thase *et al.*, 2005). A recent analysis of data pooled from six double-blind, randomized studies comparing bupropion ($n=662$), SSRIs ($n=665$) and placebo ($n=489$) also found that treatment with bupropion resulted in a greater resolution of baseline symptoms of sleepiness (hypersomnia) and fatigue than SSRI treatment (Baldwin and Papakostas, in press). Furthermore, approximately one-in-five bupropion-remitters (HAM-D17 score ≤ 7) compared to nearly one-in-three SSRI-remitters experienced residual sleepiness and fatigue at study endpoint.

Further indirect evidence for an advantage for NE- or DA-active antidepressants in the treatment of fatigue in depression comes from a study of amineptine. Rampello and coworkers (1991) reported amineptine to be more effective than minaprine, clomipramine or placebo in patients affected by “retarded depression” which they described as exhibiting anergia (lack of energy), but also other symptoms including hypokinesia, reduction of speech, hypersomnia, reduced sexual activity, psychomotor slowness and drowsiness. Dalery and colleagues (1997) found amineptine to be equally effective as fluoxetine in the treatment of MDD

overall, but superior to fluoxetine on the retardation pole of the mood, anxiety, retardation, danger scale. Vauterin and Bazot (1979) also reported amineptine to be superior to the TCA trimipramine in depressed outpatients with respect to the treatment of sadness (depressed mood), psychomotor retardation and social withdrawal.

More recently, an 8-week double-blind, randomized study compared the efficacy of the NDRI bupropion (300–450mg/day) and placebo in the treatment of 274 patients with MDD with predominant symptoms of decreased pleasure, interest and energy (Jefferson *et al.*, in press). These symptoms were defined as a minimum total score of 7 on the general interest, energy, pleasure, sexual interest, and physical energy items of the Inventory of Depressive Symptomatology (IDS). The IDS is a validated instrument designed to overcome the limitations of the HAM-D and MADRS (Rush *et al.*, 1996). Bupropion demonstrated a statistically significant improvement from baseline in both IDS-SR (self-rated) total score and IDS-C (clinician-rated) total score at week 8. Statistically significant improvements were also observed in the IDS-SR and IDS-C energy, pleasure and interest subsets, and the insomnia subset at study endpoint. Statistically significant superiority to placebo in the IDS-SR and IDS-C totals and energy, pleasure and interest symptom subsets was observed as early as week 1 and continued throughout the study. These data demonstrate that bupropion is effective in the treatment of depressed patients with predominant symptoms of decreased pleasure, interest and energy. In contrast, a study by Boyer and co-workers (2000) showed that the SSRI sertraline did not improve these symptoms until 3-to-8 weeks after treatment initiation.

These data are promising and provide support for the role of DA and NE in the treatment of core depressive symptoms associated with ‘decreased positive affect’. However, additional research is required to further clarify the potential benefits of NDRI antidepressants in this patient population.

Conclusions

There appears to be a cluster of core and highly common depressive symptoms, such as loss of pleasure, loss of interest, fatigue and loss energy and decreased motivation, that are inadequately addressed by serotonergic antidepressant therapies. Although these symptoms are variously defined, they are consistent with ‘decreased positive affect’ (Watson and Clark, 1988; Watson *et al.*, 1995b). The available pharmacological, neurobiological and clinical evidence suggest that antidepressants with a noradrenergic and dopaminergic profile of activity may offer a therapeutic benefit in the treatment of symptoms associated with ‘decreased positive affect’.

Acknowledgement

Supported by an unrestricted educational grant from GlaxoSmithkline. Acknowledgement to Julie Wilson who was the medical writer for this paper.

Sources of support

Supported by an unrestricted educational grant from GlaxoSmithkline.

Disclaimers and conflicts of interest

Professor Nutt has acted as a consultant to Pfizer, GSK, MSD, Novartis, Asahi, Organon, Cypress, Lilly, Janssen, Lundbeck, Wyeth. He has speaking honoraria (in addition to above) with Reckitt-Benckiser and Cephalon. Grants or clinical trial payments from MSD, GSK, Novartis, Servier, Janssen, Yamanouchi, Lundbeck, Pfizer, Wyeth, Organon. He has 300 shares with GSK (ex-Wellcome). Professor Demyttenaere has acted as a consultant to Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Lundbeck. He is on the speaker bureau and has accepted paid speaking engagements from Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Lundbeck, Solvay and Organon. Professor Janka has accepted paid speaking engagements in pharmaceutical industry symposia in Hungary on topics related to psychopharmacology (Astra Zeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Pfizer, G. Richter, Roche, SanofiAventis, Servier, Solvay, UCB Pharma and Wyeth). Dr Aarre has acted as a consultant to Eli Lilly and GlaxoSmithKline. He has accepted paid speaking engagements from Pfizer, Eli Lilly and GlaxoSmithKline and holds research grants from Lundbeck. He has accepted travel hospitality not related to public speaking from Eli Lilly and GlaxoSmithKline. He has also acted as a consultant to the Norwegian Medicinal Authorities. Professor Bourin is a consultant for Servier, Wyeth, GlaxoSmithKline (France), Bioproject, Pierre Fabre, Bristol-Myers Squibb (France). Professor Canonico is a consultant for GlaxoSmithKline, Eli Lilly, Pfizer, Novartis, UCB Pharma, Lundbeck and Boehringer Ingelheim. He has received research grants from Eli Lilly, Astra Zeneca, Novartis, Sigma Tau, Pfizer and Boehringer Ingelheim. He has accepted paid speaking engagements from Eli Lilly, GlaxoSmithKline, Pfizer, Merck, Novartis, Lundbeck and Bristol-Myers Squibb. He has also accepted travel hospitality not related to speaking engagements from Eli Lilly, GlaxoSmithKline, Pfizer, Novartis, Schwarz Pharma, Wyeth, UCB Pharma, Lundbeck, Amgen and Bristol-Myers Squibb. Professor Carrasco has received research grants from Pfizer, Eli Lilly and Janssen-Cilag and accepted paid speaking engagements from most pharmaceutical companies. Dr Stahl is a consultant and/or has received honoraria payments from the following companies: Asahi, Astra Zeneca, Bristol-Myers Squibb, Cephalon, Cypress Bioscience, Eli Lilly, Pierre Fabre, GlaxoSmithKline, Pfizer, Sanofi, Solvay and Wyeth Laboratories. He has also received research grants from the following pharmaceutical companies: Asahi, Astra Zeneca, Bristol-Myers Squibb, Cephalon, Cypress Bioscience, Pierre Fabre, Eli Lilly, GlaxoSmithKline, Pfizer and Wyeth Laboratories.

References

- Alonso J, Angermeyer M C, Bernet S, Bruffaerts R, Brugha T S, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro J M, Katz S J, Kessler R C, Kovess V, Lepine J P, Ormel J, Polidori G, Russo L J, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman M A, Codony M, Domingo-Salvany A, Ferrer M, Joo S S, Martinez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacin C, Romera B, Taub N, Vollebergh W A; ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project (2004a) Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* 109 (Suppl. 420): 21–27
- Alonso J, Angermeyer M C, Bernet S, Bruffaerts R, Brugha T S, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro J M, Katz S J, Kessler R C, Kovess V, Lepine J P, Ormel J, Polidori G, Russo L J, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman M A, Codony M, Domingo-Salvany A, Ferrer M, Joo S S, Martinez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacin C, Romera B, Taub N, Vollebergh W A; ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project (2004b) Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand* 109 (Suppl. 420): 38–46
- Árgyelán M, Szabó Z, Kanyó B, Tanács A, Kovács Z S, Janka Z, Pávics L (2005) Dopamine transporter availability in medication free and in bupropion treated depression: a 99mTc-TRODAT-1 SPECT study. *J Affect Disord* 89: 115–123
- Baldwin D S, Papakostas G I (in press). Symptoms of fatigue and sleepiness in major depressive disorder. *J Clin Psychiatry*
- Baker M, Dorzab J, Winokur G, Cadoret R J (1971) Depressive disease: classification and clinical characteristics. *Compr Psychiatry* 12: 354–365
- Barkham M, Rees A, Shapiro D A, Hardy G E, Stiles W, Reynolds S (1996) Dose effect relations in time-limited psychotherapy for depression. *J Consult Clin Psychol* 64: 927–935
- Barrett K (1991) Treating organic abulia with bromocriptine and lisuride: four case studies. *J Neurol Neurosurg Psychiatry* 54: 718–722
- Bodkin J A, Lasser R A, Wines J D Jr, Gardner D M, Baldessarini R J (1997) Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. *J Clin Psychiatry* 58: 137–145
- Bothwell R, Scott J (1997) The influence of cognitive variables on recovery in depressed inpatients. *J Affect Disord* 43: 207–212
- Bourin M (1999) Psychopharmacological profile of venlafaxine. *Encephale* 25: 21–25
- Boyer P, Lecrubier Y, Stalla-Bourdillon A, Fleurot O (1999) Amisulpride versus amineptine and placebo for the treatment of dysthymia. *Neuropsychobiology* 39: 25–32
- Boyer P, Tassin J P, Falissart B, Troy S (2000) Sequential improvement of anxiety, depression and anhedonia with sertraline treatment in patients with major depression. *J Clin Pharm Ther* 25: 363–371
- Bremner J D, Abrahams L M, Crupie J E, McCawley A, Proctor R C, Sathananthan S L (1984) Multicenter double-blind comparison of nomifensine and imipramine for efficacy and safety in depressed outpatients. *J Clin Psychiatry* 45: 56–59
- Bremner J D, Innis R B, Salamon R M (1997) Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. *Arch Gen Psychiatry* 54: 364–374
- Brothers L (1995) Neurophysiology of the perception of intentions by primates. In Gazzaniga, M S (ed.), *The cognitive neurosciences*. MIT Press, Cambridge, MA
- Casacalenda N, Perry J C, Looper K (2002) Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. *Am J Psychiatry* 159: 1354–1360
- Cassano P, Lattanzi L, Fava M, Navari S, Battistini G, Abelli M, Cassano G B (2005) Ropinirole in treatment-resistant depression: a 16-week pilot study. *Can J Psychiatry* 50: 357–360
- Chau D T, Roth R M, Green A I (2004) The neural circuitry of reward and its relevance to psychiatric disorders. *Curr Psychol* 6: 391–399
- Clark L A, Watson D (1991) Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *J Abnorm Psychol* 100: 316–336
- Clerc, G E, Ruimy P, Verdeau Palles J (1994) A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. The Venlafaxine French Inpatient Study Group. *Int. Clin. Psychopharmacol* 9: 139–143
- Corcoran C, Wong M L, O'Keane V (2004) Bupropion in the management of apathy. *J Psychopharmacology* 18: 133–134
- Corrigan M H, Denahan A Q, Wright C E, Ragual R J, Evans D L (2000)

- Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. *Depress Anxiety* 11: 58–65
- Croft H, Settle E Jr, Houser T, Batey S R, Donahue R M, Ascher J A (1999) A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther* 21: 643–658
- Cullum J L, Wojciechowski A E, Pelletier G, Simpson J S (2004) Bupropion sustained release treatment reduces fatigue in cancer patients. *Can J Psychiatr* 49: 139–144
- D'Aquila P S, Collu M, Gessa G L, Serra G (2000) The role of dopamine in the mechanism of action of antidepressant drugs. *Eur J Pharmacol* 405: 365–373
- Dalery J, Rochat C, Peyron E, Bernard G (1997) The efficacy and acceptability of amineptine versus fluoxetine in major depression. *Int Clin Psychopharmacol* 12 (Suppl. 3): S35–S38
- Davidson J R, Meoni P, Haudiquet V, Cantillon M, Hackett D (2002) Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. *Depress Anxiety* 16: 4–13
- Davies J, Lloyd K R, Jones I K, Barnes A, Pilowsky L S (2003) Changes in regional cerebral blood flow with venlafaxine in the treatment of major depression. *Am J Psychiatry* 160: 374–376
- Delgado P L (2000) Depression: the case for a monoamine deficiency. *J Clin Psychiatry* 61 (Suppl. 6): 7–11
- Delgado P L (2004) How antidepressants help depression: mechanisms of action and clinical response. *J Clin Psychiatry* 65 (Suppl. 4): 25–30
- Demyttenaere K, Fruyt J, Stahl S M (2004) The many faces of fatigue in major depressive disorder. *Int J Neuropsychopharmacol* 8: 93–105
- Depue R A, Collins P F (1999) Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behav Brain Sci* 22: 491–569
- Depue R A, Luciana M, Arbis P, Collins P, Leon A (1994) Dopamine and the structure of personality: relation of agonist-induced dopamine activity to positive emotionality. *J Pers Soc Psychol* 67: 485–498
- Detke M J, Wiltse C G, Mallinckrodt C H, McNamara R K, Demitrack M A, Bitter I (2004) Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol* 14: 457–470
- Di Matteo V, Di Blasi A, Di Giulio C, Esposito E (2001) Role of 5-HT(2C) receptors in the control of central dopamine function. *Trends Pharmacol Sci* 22: 229–232
- Drevets W C (1999) Prefrontal cortical-amygdala metabolism in major depression. *Ann N Y Acad Sci* 877: 614–637
- Drevets W C (2001) Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features. *Curr Opin Neurobiol* 11: 240–249
- Drevets W C, Bogers W, Raichle M E (2002) Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol* 12: 527–544
- Drevets W C, Ongur D, Price J L (1998) Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Mol Psychiatry* 3: 220–226, 190–191
- Entsuaeh A R, Huang H, Thase M E (2001) Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. *J Clin Psychiatry* 62: 869–877
- Fava M, Rush A J, Thase M E, Clayton A, Stahl S M, Pradko J F, Johnston J A (2005) 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion. J Clin Psychiatry* 7: 106–113
- Fawcett J (1994) Antidepressants: partial response in chronic depression. *Br J Psychiatry Suppl.* 26: 37–41
- Feighner J, Hendrickson G, Miller L, Stern W (1986) Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J Clin Psychopharmacol* 6: 27–32
- Feighner J P, Gardner E A, Johnston J A, Batey S R, Khayrallah M A, Ascher J A, Lineberry C G (1991) Double-blind comparison of bupropion and fluoxetine in depressed outpatients. *J Clin Psychiatry* 52: 329–335
- Garattini S (1997) Pharmacology of amineptine, an antidepressant agent acting on the dopaminergic system: a review. *Int Clin Psychopharmacol* 12 (Suppl. 3): S15–S19
- Garattini S, Mennini T (1989) Pharmacology of amineptine: synthesis and updating. *Clin Neuropharmacol* 12 (Suppl. 2): S13–S18
- Garland E J, Baerg E A (2001) Amotivational syndrome associated with selective serotonin reuptake inhibitors in children and adolescents. *J Child Adolesc Psychopharmacol* 11: 181–186
- Gaynes B N, Rush A J, Trivedi M, Wisniewski S R, Balasubramani G K, Spencer D C, Petersen T, Klinkman M, Warden D, Schneider R K, Castro D B, Golden R N (2005) A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR*D clinical trial. *Gen Hosp Psychiatry* 27: 87–96
- Gloor P, Olivier A, Quesney L F, Andermann F, Horowitz S (1982) The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Ann Neurol* 12: 129–144
- Gobert A, Rivet J M, Lejeune F, Newman-Tancredi A, Adhumeau-Auclair A, Nicolas J P, Cistarelli L, Melon C, Millan M J (2000) Serotonin(2C) receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat. *Synapse* 36: 205–221
- Gold P W, Chrousos G P (1998) The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. *Proc Assoc Am Physicians* 111: 22–34
- Goodnick P J, Goldstein B J (1998) Selective serotonin reuptake inhibitors in affective disorders – I: Basic pharmacology. *J Psychopharmacol* 12 (Suppl. B): S5–S20
- Goodnick P J, Sandoval R, Brickman A, Klimas N G (1992) Bupropion treatment of fluoxetine-resistant chronic fatigue syndrome. *Biol Psychiatry* 32: 834–838
- Green T R (1997) Bupropion for SSRI-induced fatigue. *J Clin Psychiatry* 58: 174.
- Hannonen P, Malminiemi K, Yli-Kerttula U, Isomeri R, Raponen P (1998) A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder. *Br J Rheumatol* 37: 1279–1286
- Hickie I B, Wilson A J, Wright J M, Bennet B K, Wakefield D, Lloyd A R (2000) A randomized, double-blind, placebo-controlled trial of moclobemide in patients with chronic fatigue syndrome. *J Clin Psychiatry* 61: 643–648
- Hoehn-Saric R, Lipsey J R, McLeod D R (1990) Apathy and indifference in patients on fluvoxamine and fluoxetine. *J Clin Psychopharmacol* 10: 343–345
- Hoehn-Saric R, Harris G J, Pearlson G D, Cox C S, Machlin S R, Camargo E E (1991) A fluoxetine-induced frontal lobe syndrome in an obsessive compulsive patient. *J Clin Psychiatry* 52: 131–133
- Jamerson B, Krishnan K R R, Roberts J, Krishen A, Modell J G (2003) Effect of bupropion SR on specific symptoms clusters of depression: analysis of the 31-item Hamilton Rating Scale for Depression. *Psychopharmacol Bull* 37: 67–78
- Jefferson J W, Rush A J, Nelson J C, Vanmeter S A, Krishen A, Hampton K D, Wightman D S, Modell J G (*in press*) Extended release bupropion for patients with major depressive disorder presenting with symp-

- toms of reduced energy, pleasure, and interest: findings from a randomized, double blind, placebo controlled study. *J Clin Psychiatry*
- Jouvent R, Le Houezec J, Payan C, Mikkelsen H, Fermanian J, Millet V, Dufour H (1998) Dimensional assessment of onset of action of antidepressants: a comparative study of moclobemide vs. clomipramine in depressed patients with blunted affect and psychomotor retardation. *Psychiatry Res* 79: 267–275
- Judd L L, Akiskal H S, Maser J D, Zeller P J, Endicott J, Coryell W, Paulus M P, Kunovac J L, Leon A C, Mueller T I, Rice J A, Keller M B (1998) Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *J Affect Disord* 50: 97–108
- Kavoussi R J, Segraves R T, Hughes A R, Ascher J A, Johnston J A (1997) Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psychiatry* 58: 532–537
- Kennedy N, Paykel E S (2004) Residual symptoms at remission from depression: impact on long-term outcome. *J Affect Disord* 80: 135–144
- Kennedy S H, Javanmard M, Vaccarino F J (1997) A review of functional neuroimaging in mood disorders: positron emission tomography and depression. *Can J Psychiatry* 42: 467–475
- Kiev A, Masco H L, Wenger T L, Johnston J A, Batey S R, Holloman L C (1994) The cardiovascular effects of bupropion and nortriptyline in depressed outpatients. *Ann Clin Psychiatry* 6: 107–115
- Klein D F (1974) Endogenomorphic depression: a conceptual and terminological revision. *Arch Gen Psychiatry* 31: 447–454
- Kopta S M, Howard K I, Lowry J L, Beutler L E (1994) Patterns of symptomatic recovery in psychotherapy. *J Consult Clin Psychol* 62: 1009–1116
- Learned-Coughlin S M, Bergström M, Savitcheva I, Ascher J, Schmith V D, Långström B (2003) In vivo activity of bupropion at the human dopamine transporter as measured by positron emission tomography. *Biol Psychiatry* 54: 800–805
- Lambert G, Johansson M, Agren H, Friberg P (2000) Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: evidence in support of the catecholamine hypothesis of mood disorders. *Arch Gen Psychiatry* 57: 7877–7893
- Lecrubier Y (2000) Depressive illness and disability. *Eur Neuropsychopharmacol* 10 (Suppl. 4): S439–S443
- Lecrubier Y (2002) How do you define remission? *Acta Psychiatr Scand* 106 (Suppl. 415): 7–11
- Levesque M, Bedard A, Cossette M, Parent A (2003) Novel aspects of the chemical anatomy of the striatum and its efferent projections. *J Chem Neuroanat* 26: 271–281
- Liotti M, Mayberg H S, McGinnis S, Brannan S L, Jerabek P (2002) Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression. *Am J Psychiatry* 159: 1830–1840
- Lopez-Ibor J, Guelfi J D, Pletan Y, Tournoux A, Prost J F (1996) Milnacipran and selective serotonin reuptake inhibitors in major depression. *Int Clin Psychopharmacol* 11 (Suppl. 4): 41–46
- MacHale S M, Lawrie S M, Cavanagh J T, Glabus M F, Murray C L, Goodwin G M, Ebmeier K P (2000) Cerebral perfusion in chronic fatigue syndrome and depression. *Br J Psychiatry* 176: 550–556
- Macher J P, Mirabaud C (1992) A double-blind comparison of moclobemide and amineptine in the treatment of depression in outpatients. *Psychopharmacology (Berl)* 106 (Suppl): S116–S117
- Marin R S, Fogel B S, Hawkins J, Duffy J, Krupp B (1995) Apathy: a treatable syndrome. *J Neuropsychiatry Clin Neurosci* 7: 23–30
- Massana J (1998) Reboxetine versus fluoxetine: an overview of efficacy and tolerability. *J Clin Psychiatry* 59: 8–10
- Maurice-Tison S, Verdoux H, Gay B, Perez P, Salamon R, Bourgeois M L (1998) How to improve recognition and diagnosis of depressive syndromes using international diagnostic criteria. *Br J Gen Pract* 48: 1245–1246
- Mayberg H S, Liotti M, Brannan S K, McGinnis B S, Mahurin R K, Jerabek P A, Silva J A, Tekell J L, Martin C C, Lancaster J L, Fox P T (1999) Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry* 156: 675–682
- Meyer J H, Goulding V S, Wilson A A, Hussey D, Christensen B K, Houle S (2002) Bupropion occupancy of the dopamine transporter is low during clinical treatment. *Psychopharmacology (Berl)* 163: 102–105
- Montgomery S A (1997) Reboxetine: additional benefits to the depressed patient. *J. Psychopharmacol* 11: S9–S15
- Moos R H, Cronkite R C (1999) Symptom-based predictors of a 10-year chronic course of treated depression. *J Nerv Ment Dis* 187: 360–368
- Natelson B H, Cheu J, Hill N, Bergen M, Korn L, Denny T, Dahl K (1998) Single-blind, placebo phase-in trial of two escalating doses of selegiline in the chronic fatigue syndrome. *Neuropsychobiol* 37: 150–154
- Natelson B H, Cheu J, Pareja J, Ellis S P, Policastro T, Findley T W (1996) Randomized, double-blind, controlled placebo phase-in trial of low dose phenelzine in chronic fatigue syndrome. *Psychopharmacology (Berl)* 124: 226–230
- Nelson J C, Clary C M, Leon A C (2005) Symptoms of late life depression: frequency and change during treatment. *Am J Geriatric Psychiatry* 13: 520–526
- Nemeroff C B, Schatzberg A F, Goldstein D J, Detke M J, Mallinckrodt C, Lu Y, Tran P V (2002) Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull* 36: 106–132
- Nierenberg A A, DeCocco L M (2001) Definitions of antidepressant treatment response, remission, non-response, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J Clin Psychiatry* 62 (Suppl. 16): 5–9
- Nierenberg A A, Keefe B R, Leslie V C, Alpert J E, Pava J A, Worthington III J J, Rosenbaum J F, Fava M (1999) Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry* 60: 221–225
- Opbroek A, Delgado P L, Laukes C, McGahuey C, Katsanis J, Moreno F A, Manber R (2002) Emotional blunting associated with SSRI-induced sexual dysfunction: do SSRIs inhibit emotional responses? *Int J Neuropsychopharmacol* 5: 147–151
- Opdyke K S, Reynolds III C F, Frank E, Begley A E, Buysse D J, Drew M A, Mulsant B H, Shear M K, Mazumdar S, Kupfer D J (1996–1997) Effect of continuation treatment on residual symptoms in late-life depression: how well is ‘well’. *Depress Anxiety* 4: 312–319
- Ormel J, Vonkorff M, Oldehinkel A J, Simon G, Tiemens B G, Üstun T B (1999) Onset of disability in depressed and non-depressed primary care patients. *Psychol Med* 29: 847–853
- Papakostas G I (2006) Dopaminergic-based pharmacotherapies for depression. *Eur Neuropsychopharmacol* (Epub ahead of print)
- Paykel E S (2002) Achieving gains beyond response. *Acta Psychiatr Scand* 106 (Suppl. 415): 12–17
- Paykel E S, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A (1995) Residual symptoms after partial remission: an important outcome in depression. *Psychol Med* 25: 1171–1180
- Pearson S D, Katzelnick D J, Simon G E, Manning W G, Helstad C P, Henk H J (1999) Depression among high utilizers of medical care. *J Gen Intern Med* 14: 461–468
- Petersen T, Papakostas G I, Pasternak M A, Kant A, Guyker W M, Iosifescu D V, Yeung A S, Nierenberg A A, Fava M (2005) Empirical testing of two models for staging antidepressant treatment resistance. *J Clin Psychopharmacol* 25: 336–341

- Prisco S, Esposito E (1995) Differential effects of acute and chronic fluoxetine administration on the spontaneous activity of dopaminergic neurones in the ventral tegmental area. *Br J Pharmacol* 116: 1923–1931
- Rampello L, Nicoletti G, Raffaele R (1991) Dopaminergic hypothesis for retarded depression: a symptom profile for predicting therapeutical responses. *Acta Psychiatr Scand* 84: 552–554
- Rampello L, Nicoletti G, Raffaele R, Drago F (1995) Comparative effects of amitriptyline and amineptine in patients affected by anxious depression. *Neuropsychobiology* 31: 130–134
- Reimherr F W, Cunningham L A, Batey S R, Johnston J A, Ascher J A (1998) A multicenter evaluation of the efficacy and safety of 150 and 300 mg/d sustained-release bupropion tablets versus placebo in depressed outpatients. *Clin Ther* 20: 505–551
- Rush A J, Trivedi M H (1995) Treating depression to remission. *Psychiatr Ann* 25: 704–709.
- Rush A J, Gullion C M, Basco M R, Jarrett R B, Trivedi M H (1996) The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* 26: 477–486
- Salamone J D (1996) The behavioural neurochemistry of motivation: methodological and conceptual issues in studies of the dynamic activity of nucleus accumbens dopamine. *J Neurosci Methods* 64: 137–149
- Salamone J D, Correa M, Mingote S, Weber S M (2003) Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. *J Pharmacol Exp Ther* 305: 1–8
- Schildkraut J J (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* 122: 509–522
- Schmidt K, Nolte-Zenker B, Patzer J, Bauer M, Schmidt L G, Heinz A (2001) Psychopathological correlates of reduced dopamine receptor sensitivity in depression, schizophrenia and opiate and alcohol dependence. *Pharmacopsychiatry* 34: 66–72
- Shelton R C, Tomarken A J (2001) Can recovery from depression be achieved? *Psych Serv* 52: 1469–1478
- Sitland-Marken P A, Wells B G, Froemming J H, Chu C C, Brown C S (1990) Psychiatric applications of bromocriptine therapy. *J Clin Psychiatry* 51: 68–82
- Smith D, Dempster C, Glanville J, Freemantle N, Anderson I (2002) Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. *Br J Psychiatry* 180: 396–404
- Spijker J, Bijl R V, de Graaf R, Nolen W A (2001) Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS) *Acta Psychiatr Scand* 103: 122–130
- Stahl S M, Zhang L, Damatarca C, Grady M (2003) Brain circuits determine destiny in depression: a novel approach to psychopharmacology of wakefulness, fatigue and executive dysfunction in major depressive disorder. *J Clin Psychiatry* 64 (Suppl. 14): 6–17
- Stahl S M, Pradko J F, Haight B R, Modell J G, Rockett C B, Learned-Coughlin S (2004) A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. *Prim Care Companion, J Clin Psychiatry* 6: 159–166
- Stewart J W, Quitkin F, Fyer A, Rifkin A, McGrath P, Liebowitz M, Rosnick L, Klein D F (1980) Efficacy of desipramine in endogenomorphically depressed patients. *J Affect Disord* 2: 165–176
- Suh T, Gallo J J (1997) Symptom profiles of depression among general medical service users compared with specialty mental health service users. *Psychol Med* 27: 1051–1063
- Swindle R, Kroenke K, Braun L A (2001) Energy and improved workplace productivity in depression. In Farquahar I, Summers K, Sorkin A (eds), *Investing in health: the social and economic benefits of health care innovation*, vol. 14. Elsevier Science Ltd, New York.
- Thase M E (2003) Effectiveness of antidepressants: comparative remission rates. *J Clin Psychiatry* 64 (Suppl. 2): 3–7
- Thase M E, Entsuah A R, Rudolph R L (2001) Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 178: 234–241
- Thase M E, Trivedi, M H, Rush A J (1995) MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology* 12: 185–219.
- Thase M E, Haight B R, Richard N, Rockett C B, Mitton M, Modell J G, VanMeter S, Harriett A E, Wang Y (2005) Remission rates following antidepressant therapy with bupropion or selective reuptake inhibitors: a meta-analysis of original data from 7 randomised controlled trials. *J Clin Psychiatry* 66: 974–981
- Thase M E, Simons A D, McGeary J, Cahalane J F, Hughes C, Harden T, Friedman E (1992) Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. *Am J Psychiatry* 149: 1046–1052
- Tomarken A J, Dichter G S, Freid C, Addington S, Shelton R C (2004) Assessing the effects of bupropion SR on mood dimensions of depression. *J Affect Disord* 78: 235–241
- Trivedi M H, Rush A J, Carmody T J, Donahue R M, Bolden-Watson C, Houser T L, Metz A (2001) Do bupropion SR and sertraline differ in their effects on anxiety in depressed patients? *J Clin Psychiatry* 62: 776–781
- Trivedi M H, Rush A J, Wisniewski S R, Warden D, McKinney W, Downing M, Berman S R, Farabaugh A, Luther J F, Nierenberg A A, Callan J A, Sackeim H A (2006) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 163: 28–40
- Tylee A T, Freeling P, Kerry S (1993) Why do general practitioners recognize major depression in one woman patient yet miss it in another? *Br J Gen Pract* 43: 327–330
- Tylee A, Gastpar M, Lepine J P, Mendlewicz J. for the DEPRES Steering Committee (1999) DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. *Int Clin Psychopharmacol* 14: 139–151
- Vauterin C and Bazot M (1979) A double-blind controlled trial of amineptine versus trimipramine in depression. *Curr Med Res Opin* 6: 101–106
- Videbech P (2000) PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. *Acta Psychiatr Scand* 101: 11–20
- Volkow N D, Ding Y S, Fowler J S, Wang G J, Logan J, Gatley J S, Dewey S L, Ashby C, Lieberman J, Hitzemann R, Wolf A P (1995) Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. *Arch Gen Psychiatry* 52: 456–463
- Volkow N D, Wang G J, Fischman M W, Foltin R W, Fowler J S, Abumrad N N, Vitkun S, Logan J, Gatley S J, Pappas N, Hitzemann R, Shea C E (1997) Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 386: 827–830
- Volkow N D, Wang G J, Fowler J S, Gatley S J, Logan J, Ding Y S, Hitzemann R, Pappas N (1998) Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *Am J Psychiatry* 155: 1325–1331
- Watson D, Clark L A (1988) Positive and negative affectivity and their relation to anxiety and depressive disorders. *J Abnormal Psychol* 97: 346–353
- Watson D, Tellegen A (1985) Toward a consensual structure of mood. *Psychol Bull* 98: 219–235

-
- Watson D, Clark L A, Tellegen A (1984) Cross cultural convergence in structure of mood: a Japanese replication and a comparison with US findings. *J Personal Soc Psychobiol* 47: 127–144
- Watson D, Weber K, Assenheimer J S, Clark L A, Strauss M E, McCormick R A (1995b) Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptoms scales. *J Abnorm Psychol* 104: 3–14
- Watson D, Clark L A, Weber K, Assenheimer J S, Strauss M E, McCormick R A (1995a) Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult and patient samples. *J Abnorm Psychol* 104: 15–25
- Weihs K L, Settle E C Jr, Batey S R, Houser T L, Donahue R M, Ascher J A (2000) Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J Clin Psychiatry* 61: 196–202
- Weisler R H, Johnston J A, Lineberry C G, Samara B, Branconnier R J, Billow A A (1994) Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 14: 170–179
- White P D, Cleary K J (1997) An open study of the efficacy and adverse events of moclobemide in patients with the chronic fatigue syndrome. *Int Clin Psychopharmacol* 12: 47–52
- Willner P (1983a) Dopamine and depression: a review of recent evidence. I. Empirical studies. *Brain Res* 287: 211–224
- Willner P (1983b) Dopamine and depression: a review of recent evidence. II. Theoretical approaches. *Brain Res* 287: 225–236
- Willner P (1983c) Dopamine and depression: a review of recent evidence. III. The effects of antidepressant treatments. *Brain Res* 287: 237–246
- Willner P (1995) Animal models of depression: validity and applications. *Adv Biochem Psychopharmacol* 49: 19–41
- Willner P (2000) Dopaminergic mechanisms in depression and mania. In Watson S (ed.), *Psychopharmacology: the fourth generation of progress*. Lippincott, Williams and Wilkins, New York (online edition)
- Wise R A (1982) Neuroleptics and operant behaviour: the anhedonia hypothesis. *Behav Brain Sci* 5: 39–87
- Zung W W, Brodie H K, Fabre L, McLendon D, Garver D (1983) Comparative efficacy and safety of bupropion and placebo in the treatment of depression. *Psychopharmacology (Berl)* 79: 343–347