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

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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

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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.

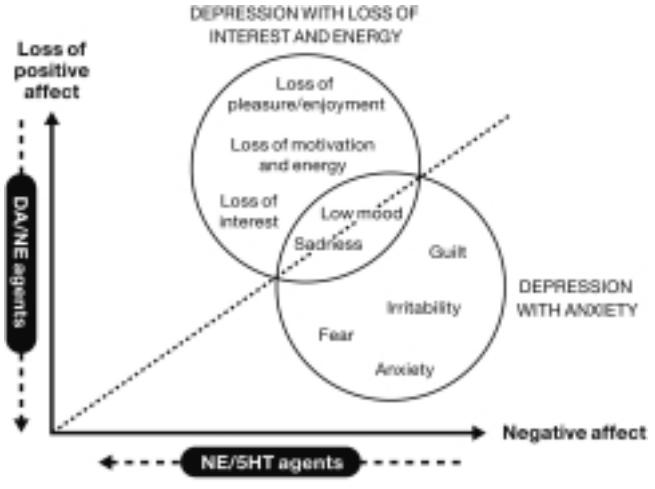

Figure 1 Hypothetical model showing differential actions of antidepressant agents on symptoms of positive and negative affect

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

20 mg/day fluoxetine for 8 weeks, the most common residual symptoms in patients who achieved remission (HAM-D ≤ 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 (150–300 mg/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. hypofunction) 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

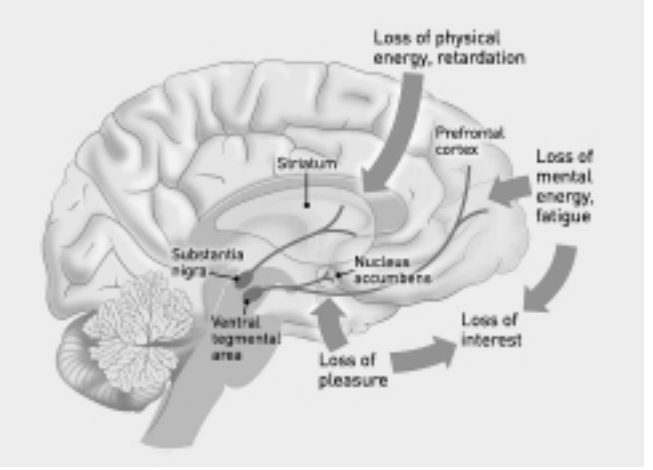

Figure 2 Schematic diagram of brain dopamine systems and possible sites of symptom generation

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) (Ki 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 anecdoctal 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 300 mg/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 (300–400 mg/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 (300–450 mg/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'.

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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-Benkiser 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, Egis, 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.

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