Major depressive disorder (MDD) is a common medical illness affecting millions worldwide. Despite their widespread use since the 1950s and 1960s, the ‘downstream’ mechanism by which antidepressants ultimately exert their therapeutic effects remains elusive. In addition, except for a few exceptions such as episode severity and the presence of comorbid Axis-I or Axis-III disorders, biological or clinical characteristics which can accurately quantify the risk of poor treatment outcome are lacking, as are factors which could help patients and clinicians select treatment options that would result in superior outcome. The identification of such markers, termed ‘surrogate’ markers, could help shed further insights into what constitutes illness and recovery, help identify molecular targets for the development of future antidepressants, and lead the way to the design and refinement of a personalized medicine treatment model for MDD. In the following text, several major areas (‘leads’) where evidence exists regarding the presence of surrogate markers of efficacy outcome in MDD will be briefly reviewed. Leads include evidence from the role of demographic and clinical factors as surrogate markers, to the role of various biological markers including genotype, brain functional imaging, electroencephalography, dichotic listening, and molecular biology and immunology. The purpose of this work is to focus selectively on areas where there have been findings, as opposed to conducting an exhaustive literature review of studies which have failed to yield any significant breakthrough in our knowledge.

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Overview and definition of surrogate markers

Major depressive disorder (MDD) is a common medical illness affecting millions worldwide. Results from the 2003 National Comorbidity Replication study found that the lifetime prevalence of MDD among American adults is 16.2%, ranking it among the most common and costly medical illnesses (Kessler et al. 2003). Although to date, numerous agents have been developed and marketed for the treatment of MDD, studies have shown that antidepressant monotherapy results in remission rates of approximately 33% at best (Papakostas & Fava, 2006; Petersen et al. 2005; Trivedi et al. 2006). In addition, despite their widespread use since the 1950s and 1960s, the ‘downstream’ mechanism by which these drugs ultimately exert their therapeutic effects remains elusive. Furthermore, except for a few exceptions such as episode severity and the presence of comorbid Axis-I or Axis-III disorders, biological or clinical characteristics which can accurately quantify the risk of poor treatment outcome are lacking, as are factors which could help patients and clinicians select treatment options that would result in superior outcome. Clearly, there is an urgent need to develop safer, better tolerated, and more effective treatments for MDD, to better understand the downstream effects of these treatments, and to develop better prognostic markers for these treatments. The identification of such markers, termed ‘surrogate’ markers, including predictors, moderators, and mediators, could help shed further insights into what constitutes illness and recovery, help identify molecular targets for the development of...
future antidepressants, and lead the way to the design and refinement of a personalized medicine treatment model for MDD.

Whether clinical, demographic, or biological in nature, a surrogate marker of efficacy outcome in MDD can have one of several properties (Kraemer et al. 2002):

1. A surrogate marker can serve as a predictor (Fig. 1) when the presence and/or magnitude of that marker temporally precedes and is statistically correlated to an efficacy outcome (e.g. greater episode severity before treatment predicts poorer outcome). Such outcomes can include the resolution of depressive symptoms during treatment, the time-course of symptom reduction, as well as dichotomous outcomes such as response and remission rates. These markers are measured at one time-point, usually at baseline. Such markers can derive from any type of study (open-label as well as double-blind).

2. A surrogate marker can serve as a moderator (Fig. 2) if it is statistically correlated to differential efficacy outcome with one therapy vs. another (e.g. although two drugs are equally efficacious in a clinical trial, the presence of a marker in patients confers superior outcome during the course of the trial to one drug vs. another). Similar to a predictive marker, these markers are measured at one time-point, usually at baseline. Unlike predictors and mediators, such markers can only derive from comparator studies (preferably double-blind rather than open-label).

3. A surrogate marker can serve as a mediator (Fig. 3) of efficacy if the marker represents a change in value during treatment and is statistically correlated to an efficacy outcome (e.g. a change in a biological marker during the first 8 wk of treatment is correlated with outcome at week 8). Unlike a marker which is only a predictor or moderator, these markers always involve at least two different over time – usually at baseline and during the trial. Such markers can derive from any type of study (open-label as well as double-blind).

It is important to keep in mind that a surrogate marker can possess more than one of these three qualities. For instance, if change in a biological variable in the first 24 h of therapy was correlated with superior outcome with treatment A vs. treatment B, two otherwise equally efficacious therapies, then that variable would serve as a predictor (since it temporally precedes outcome), a moderator (since it is associated with differential outcome), and a mediator (since it represents a change in value during treatment). In the following text, several major areas (‘leads’) where evidence exists regarding the presence of surrogate markers of efficacy outcome in MDD will be briefly reviewed. The purpose of this work will be to selectively focus on areas where there have been findings, as opposed to conducting an exhaustive literature review of studies which have failed to yield any significant breakthrough in our knowledge.

Clinical and demographic factors

The presence of Axis-III comorbidity, whether general (Ioșifescu et al. 2003) or specific including
hypercholesterolaemia (Sonawalla et al. 2002), obesity (Papakostas et al. 2004a), cardiovascular risk factors (Iosifescu et al. 2005a; Papakostas et al. 2005a), folate deficiency (Fava et al. 1997a; Papakostas et al. 2005a,b), and brain white-matter changes (Alexopoulos et al. 2008; Iosifescu et al. 2006; Papakostas et al. 2005a) have been linked to poorer outcome during treatment with selective serotonin reuptake inhibitors (SSRIs). Hypercholesterolaemia (Papakostas et al. 2003a), but not overall Axis-III comorbidity burden (Papakostas et al. 2003b) have also been linked to lower chances of responding to the tricyclic antidepressant (TCA) nortriptyline in MDD.

The presence of anxiety symptoms or a comorbid anxiety disorder has also been linked to poorer outcome during SSRI therapy. For example, MDD patients presenting with at least one comorbid anxiety disorder were less likely to improve during treatment with the SSRI fluoxetine (Fava et al. 1997b), but not the SSRI sertraline (Hirschfeld et al. 1998) in two separate trials. In parallel, although a number of earlier studies (Feiger et al. 2003; Lenze et al. 2003; Sir et al. 2005; Tollefson et al. 1994) which had defined anxious depression as the presence of a high burden of comorbid anxiety symptoms did not detect a statistically significant relationship between the presence of these symptoms and poorer outcome during SSRI therapy, recent evidence stemming from levels 1 and 2 of the large STAR*D study do suggest markedly lower remission rates for patients with vs. without anxious MDD following treatment with either first-line (citalopram) or second-line treatment strategies (switching to antidepressants vs. augmentation or combination strategies) (Fava et al. 2008). Interestingly, a recent analysis involving 10 randomized, double-blind clinical trials comparing the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion with a SSRI also revealed superior outcome among patients with anxious MDD following treatment with a SSRI than bupropion (Papakostas et al. 2008a) (moderator).

Furthermore, although Sir et al. (2005) and Davidson et al. (2002) reported that patients with anxious MDD were not less likely to experience symptom improvement following treatment with the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine than those without, Silvestone & Salinas (2001) reported slower symptom reduction among venlafaxine-treated MDD patients with comorbid generalized anxiety disorder (GAD) than those without, while results of STAR*D also reported patients with anxious depression were significantly less likely to experience remission during treatment with venlafaxine than those without (Fava et al. 2008). In general, however, hormonal status as opposed to the presence of anxious MDD (Fava et al. 2008) did not show difference in efficacy between the SNRI venlafaxine and the SSRI sertraline in anxious MDD and appears to be more relevant with respect to differentiating the antidepressant effects of the SSRIs and SNRIs. Specifically, in one pooled analysis, post-menopausal depressed women not on hormone replacement therapy were reported to be much more likely to attain remission of MDD following treatment with the SNRI venlafaxine than a SSRI than either pre-menopausal women or post-menopausal women on hormone replacement therapy (Thase et al. 2005). Although a similar report for the SNRI duloxetine vs. SSRIs has not been published yet, Kornstein et al. (2006) did not find either age or gender influenced efficacy outcome following treatment with the SNRI duloxetine.

Although some reports have suggested that MDD patients who present with comorbid anxiety disorders or with a greater burden of anxiety symptoms may be less likely to experience the benefits of treatment with a TCA and/or monoamine oxidase inhibitor (MAOI) than those without (Flin & Rifat, 1997; Grunhaus et al. 1986, 1988), the majority of studies focusing on the use of these older agents do not report a statistically significant treatment predictive effect as far as the MAOIs (Angst et al. 1993; Delini-Stula et al. 1995; Liebowitz et al. 1988, 1990; Robinson et al. 1985) or TCAs (Angst et al. 1993; Delini-Stula et al. 1995; Friedman et al. 1995; Hirschfeld et al. 1998; Lenze et al. 2003; Liebowitz et al. 1988; Quitkin et al. 1988, 1990; Robinson et al. 1985; Russell et al. 2001; Simon et al. 1998; Tollefson et al. 1994) are concerned. It appears that the presence of a different MDD subtype, that of atypical depression, is more relevant with respect to differentiating TCA/MAOI therapy than that of anxious depression. More specifically, the presence of atypical MDD has been shown to predict a greater likelihood of clinical response to treatment with the MAOI phenelzine than the TCA imipramine (Quitkin et al. 1990, 1991) (moderator).

Episode severity has also been reported to serve as a moderator of efficacy outcome in some MDD studies. For instance, greater MDD severity was found to predict a greater likelihood of attaining remission of depression following treatment with the SSRI escitalopram than several other SSRIs (fluoxetine, sertraline, paroxetine, citalopram) in MDD (Kennedy et al. 2006, 2009) (moderator). Similarly, greater episode severity was found to predict a greater likelihood of attaining remission of depression following treatment with the SNRI duloxetine (Thase et al. 2007), and the SNRI venlafaxine (Schmitt et al. 2009) than SSRIs in
MDD. In addition to episode severity, an early change (reduction) in depressive symptomatology has also been found to serve as both a predictor (temporally preceding outcome) and mediator (indicating a relationship between change in value during the course of therapy and outcome at endpoint) of outcome (Baldwin et al. 2009; Nierenberg et al. 1995, 2000; Stassen et al. 1996; Taylor et al. 2006a, b).

Although studies showing a robust impact of the presence of Axis-II, cluster B personality disorder comorbidity on treatment outcome involving the use of newer agents (SSRIs, SNRIs, NDRI bupropion), have not been published to date, two studies do report poorer outcome among patients with MDD who also present with a comorbid cluster C-type Axis-II disorder during TCA therapy than those without (Papakostas et al. 2003c; Peselow et al. 1992). In addition, certain elements of temperament including novelty seeking, harm avoidance and reward dependence were found to predict outcome following TCA therapy (Joyce et al. 1994), but not another (Sato et al. 1999) study. Finally, Nelson & Cloninger (1995) reported reward dependence and harm avoidance to predict response to treatment with the 5-HT2 receptor antagonist nefazodone in MDD. This was confirmed shortly thereafter using a larger much dataset (Nelson & Cloninger, 1997). However, the predictive power of neuroticism in the latter study accounted for a mere 1.1% of the total variance in outcome of MDD during antidepressant treatment, bringing into question its clinical relevance.

A number of other symptoms of MDD have also been linked to poorer prognosis during treatment with a SSRI, such as hopelessness (Papakostas et al. 2007), executive dysfunction (Alexopoulos et al. 2005), physical symptoms of depression (pain, fatigue, anxiety, gastrointestinal symptoms) (Burns et al. 1995; Denninger et al. 2006; Papakostas et al. 2004a, b, 2008b), and psychomotor retardation (Burns et al. 1995; Caligiuri et al. 2003; Taylor et al. 2006a, b). Interestingly enough, the presence of physical symptoms of depression has not been found to confer poorer prognosis during TCA therapy (Papakostas et al. 2003d).

Studies described above examining predictors of outcome of MDD during antidepressant treatment involve analyses focusing on one or two elements at a time, which does not allow investigators to compare the relative predictive value of each individual element against other potentially relevant factors and, thus, control for any confounding. More recently, Trivedi et al. (2006) examined data from level 1 of STAR*D (open-label treatment with the SSRI citalopram, up to 60 mg for up to 14 wk). Demographic (i.e. age, gender, race, sociodemographic variables) and clinical (age of onset of illness, episode duration, psychiatric and medical comorbidity) variables were entered into the regression model. Participants who were Caucasian, female, employed, or had higher levels of education/income were more likely to experience the benefits of treatment while those with longer depressive episodes, Axis-I (especially anxiety disorders and or drug abuse) and Axis-III disorders, and lower baseline psychosocial functioning and quality of life were associated with poorer outcome.

Genotype

Genotype, most likely, represents the largest and fastest growing area in the predictor and moderator literature, with the majority of reports focusing on genes related to the monoamine neurotransmitters [serotonin (5-HT), norepinephrine (NE), and dopamine (DA)], and their function including tryptophan hydroxylase (TPH; involved in 5-HT synthesis), the 5-HT transporter (5-HTT), various 5-HT receptors (5-HT1, 5-HT2, etc.), monoamine oxidase (MAO), and catechol-O-methyltransferase (COMT).

More specifically, a total of five reports focus on the potential role of a certain variant of the TPH gene (A218C) and SSRI treatment outcome, with three (Ham et al. 2007; Serretti et al. 2001a, b) out of six (Hong et al. 2006; Kato et al. 2007; Yoshida et al. 2002a) demonstrating a statistically significant predictive role. With respect to 5-HTT, some (Arias et al. 2003; Bozina et al. 2008; Durham et al. 2004; Kato et al. 2006; Kronenberg et al. 2007; Ng et al. 2006; Rausch et al. 2002; Serretti et al. 2001a; Smeraldi et al. 1998; Yu et al. 2002; Zanardi et al. 2000, 2001) but not other (Dmitrzak-Wegrzorz et al. 2007; Kim et al. 2000; Kraft et al. 2005; Minov et al. 2001; Yoshida et al. 2002b) reports have identified a link between the presence of a specific (insertion/deletion) polymorphism in the promoter region of the serotonin transporter gene (5-HTTPR) and outcome (response, remission, change in symptom scores) during SSRI treatment. Conflicting reports also exist with respect to outcome following treatment with a TCA (Dmitrzak-Wegrzorz et al. 2007; Tsapakis et al. 2003), although separate studies confirm a relationship between 5-HTTPR genotype and outcome following treatment with the SNRI venlafaxine (Choi et al. 2007), and the serotonin-norepinephrine receptor antagonist (SNRA) mirtazapine (Kang et al. 2007).

There have been attempts to reconcile discrepant findings regarding the predictive role of 5-HTTPR polymorphisms and treatment outcome in MDD, with a number of pooled meta-analyses confirming a
predictive role, more so for Caucasian than Asian patients (Kato & Serretti, 2010; Serretti et al. 2006, 2007; Smits et al. 2004). Subsequently, however, Kraft et al. (2007) and Hu et al. (2007) did not find an association between 5-HTTPR genotype and outcome following treatment with the SSRI citalopram in STAR*D ($n=1914$), although a subsequent analysis suggested a statistically significant association for Caucasians only (Mrazek et al. 2009). Similarly, there have been conflicting reports regarding the relationship between 5-HT$_2$ receptor genotype and SSRI outcome, with two (Choi et al. 2007; Kato et al. 2006) but not a third (Sato et al. 2002) study demonstrating the presence of a specific gene variant (A1438G) to predict poorer response to SSRIs in MDD. It would be interesting to examine whether confounding by genetic, clinical, or demographic factors (age, race, gender) is responsible for the discrepancy in findings among genetic studies, thus far, reviewed.

Relatively fewer reports have focused on genes coding for proteins not directly related to the monoaminergic system. Among these, most notable are studies which have demonstrated a statistically significant relationship between the presence a variant of BDNF (Zou et al. 2010), TREK1 (coding for a potassium channel; Perlis et al. 2008), GRIK4 (coding for a kainic acid-type glutamate receptor; Paddock et al. 2007), angiotensin-converting enzyme and receptor II (Bondy et al. 2005) and FKBP5 genes (coding for a protein which modulates the glucocorticoid receptor; Lekman et al. 2008) and SSRI treatment outcome. As with clinical and demographic variables, when examining genetic predictors in univariate fashion it is not possible compare the relative predictive value of each individual element against other potential predictors and, thus, control for any confounding. In order to address this, McMahon et al. (2006) conducted an analysis of numerous candidate genes as potential predictors of response to the SSRI citalopram, open-label citalopram ($n=1953$). Of more than 60 genes investigated, only genetic variation at the locus of the 5-HT$_1$ receptor gene was found to consistently predict outcome (McMahon et al. 2006). Other approaches have, more recently, been undertaken in order to attempt to ‘enhance’ the ‘predictive ability’ of individual (i.e. univariate) genotype variables with respect to acute-phase treatment outcome in MDD including the use of genome-wide association studies (Ising et al. 2009) as well as utilizing the interaction of genetic and other (i.e. serum-based) biomarkers (Horstmann et al. 2010).

Even fewer studies have examined whether genotype can serve as a moderator of response to various antidepressants. Of these, most notable are two reports, one of which reported a statistically significant relationship between variants in the gene coding for the G-protein $\beta_{3}$-subunit and differential response to the TCA nortriptyline vs. the SSRI fluoxetine in adult MDD patients aged $\leq 25$ yr (Joyce et al. 2003), the other a statistically significant relationship between variants in the gene coding for COMT and differential response to the SSRI paroxetine vs. the SNRI mirtazapine (Szegedi et al. 2005). Although interesting, these are preliminary and have not yet been replicated.

**Brain functioning and metabolism**

Positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and functional magnetic resonance imaging (fMRI) have all been used to study whether baseline characteristics or changes in brain functioning and metabolism correlate with symptom improvement following treatment with standard antidepressants. Mayberg et al. (2000), for example, reported a correlation between an increase in brainstem and dorsal cortical metabolism (prefrontal, parietal, anterior cingulate, posterior cingulate), or a decrease in limbic and striatum metabolism (subgenual cingulate, hippocampus, insula, pallidum) as measured by PET and symptom improvement following treatment with the SSRI fluoxetine. In 2002, Mayberg et al. (2002) reviewed studies published to date examining the correlation between changes in brain metabolism patterns and symptom resolution in MDD following treatment with standard antidepressants, and concluded that normalization of frontal hypometabolism as a correlate of symptom improvement was the most consistent finding. Subsequently, Little et al. (2005), examined for differences in brain metabolism patterns at baseline (predictor or moderator) as measured by PET and clinical outcome between the NDRI bupropion and the SNRI venlafaxine. For the most part, similar parameters correlated with symptom improvement for both agents (frontal and left temporal hypometabolism), although some differences did emerge (compared to control subjects, bupropion responders ($n=6$) also had cerebellar hypermetabolism, whereas venlafaxine responders showed bilateral temporal and basal ganglia hypometabolism). This study, also notable for its small sample size, has yet to be replicated.

Studies involving the use of fMRI have been instrumental in linking changes in brain metabolism during the performance of cognitive tasks and treatment outcome in MDD. Specifically, several reports have demonstrated a link between increases in
metabolism in the anterior cingulate cortex following the presentation of visual or auditory stimuli designed to induce affect (either happy or sad) at baseline and symptom improvement during antidepressant and/or psychotherapy treatment (Chen et al. 2007; Davidson et al. 2003; Fu et al. 2004, 2007, 2008). In fact, a relationship between the change (reduction in this case) in visual-stimulus-evoked anterior cingulate cortex activation during the course of treatment and greater symptom improvement (moderator) was also reported in one study (Fu et al. 2004).

With the use of MRS techniques, Renshaw et al. (2001) demonstrated that depressed women with low brain purine levels at baseline were more likely to experience the clinical benefit of the SSRI antidepressant fluoxetine, suggesting that an increase in brain adenosine triphosphate levels may be associated with an antidepressant response. An earlier MRS-based study had also linked low choline to creatine resonance in the basal ganglia of depressed subjects with treatment response to the SSRI fluoxetine (Renshaw et al. 1997). More recently, also with the use of MRS techniques, Iosifescu et al. (2008) confirmed both earlier findings by reporting a correlation between an increase in brain nucleoside triphosphate levels or a decrease in phosphocreatine levels and symptom improvement during augmentation of SSRIs with triiodothyronine, suggesting that an increase in brain adenine triphosphate levels may be associated with an antidepressant response. An earlier MRS-based study had also linked low choline to creatine resonance in the basal ganglia of depressed subjects with treatment response to the SSRI fluoxetine (Renshaw et al. 1997). More recently, also with the use of MRS techniques, Iosifescu et al. (2008) confirmed both earlier findings by reporting a correlation between an increase in brain nucleoside triphosphate levels or a decrease in phosphocreatine levels and symptom improvement during augmentation of SSRIs with triiodothyronine, findings which further suggest a re-normalization of brain bioenergetics in treatment responders vs. non-responders. Thus, the confluence of evidence from PET, fMRI, and MRS studies suggests a significant relationship between brain metabolism patterns (or their changes) and symptom improvement in MDD.

Quantitative electroencephalography (QEEG)

QEEG involves the analysis of electroencephalographic (EEG) recordings from multiple scalp areas with the use of specialized computer software. Several measures are derived, some of which have been shown to correlate with symptom improvement during antidepressant treatment. One such measure includes cordance. Cordance is a measure which is derived from various brain EEG readings [specifically it is a combination of absolute power (the power of a frequency band) and relative power (the percentage of power in a frequency band compared to the total power across all frequency bands)] (Hunter et al. 2007; Leuchter et al. 1994). Cordance of frontal theta band (4–8 Hz) measurements has repeatedly been shown to correlate with treatment response in MDD. Specifically, a decrease in prefrontal lead theta cordance during the first week of treatment of MDD has been found to predict greater symptom improvement following 3–9 wk of additional therapy, a finding that has been replicated with several different antidepressant agents (SSRIs, SNRIs, other agents) (Bares et al. 2007; Cook et al. 2002, 2005). In contrast, an increase in prefrontal theta cordance during the first week of treatment has been linked to an increased likelihood of placebo response; suggesting that prefrontal theta cordance may serve as a differential predictive mediator of response to standard antidepressants vs. placebo (Leuchter et al. 2002). Interestingly enough, in a subsequent study, Hunter et al. (2006) also reported a decrease in theta cordance from prefrontal leads during the week immediately preceding the initiation of treatment with an antidepressant or placebo to be related to the likelihood of experiencing symptom resolution following 9 wk of antidepressant but not placebo treatment (moderator of response).

In summary, changes in prefrontal theta cordance during the first week of treatment in MDD appear to serve as a mediator and predictor of response to antidepressants but not placebo. Although the exact physiological relevance of this finding remains, at present, unclear, several converging lines of evidence suggest it may serve as a proxy for changes in underlying prefrontal cortex metabolism (see Hunter et al. 2007 for further details).

Antidepressant treatment response index (ATR), originally developed by Iosifescu et al. (2005b), is a different QEEG-derived measure. ATR was recently evaluated as a moderator of symptom improvement among MDD patients treated with the SSRI escitalopram for 1 wk followed by 7 wk of treatment with either (1) continued escitalopram therapy, (2) a switch to the NDRI bupropion, or (3) bupropion augmentation (Leuchter et al. 2009). QEEG ATR pattern changes after the first week of therapy differentiated between patients who went on to experience symptom improvement during either continued escitalopram or bupropion monotherapy, but not bupropion augmentation. This study has yet to be replicated, while elucidating the underlying physiological relevance of this finding requires further study.

Loudness dependence of auditory-evoked potentials (LDAEP)

LDAEPs are EEG recordings measured from the area of the primary auditory cortex following the administration of an auditory stimulus (Hunter et al. 2007). A ‘strong’ LDAEP suggests that evoked potentials following such a stimulus are dependent on the loudness of the stimulus, while a ‘weak’ LDAEP suggests
those with ‘weak’ LDAEP (Gallinat et al. 2000; Linka et al. 2004; Mulert et al. 2002, 2007; Paige et al. 1994), while in a separate trial comparing the SSRI citalopram with the norepinephrine reuptake inhibitor (NRI) reboxetine, patients with ‘strong’ LDAEP were more likely to respond to citalopram than reboxetine therapy while patients with ‘weak’ LDAEP demonstrated the opposite pattern of response (more likely to response to reboxetine than citalopram treatment) (Juckel et al. 2007). This finding has yet to be replicated.

**Brain functional asymmetry (dichotic listening)**

Dichotic listening involves the presence of perceived differences in perception (perceptual asymmetry) when auditory stimuli (sounds) are simultaneously presented to both ears (dichotic listening tasks). Bruder et al. (1990) first reported a relationship between perceptual asymmetry following dichotic listening tasks at baseline and outcome during TCA therapy, such that patients with a left-ear advantage were significantly more likely to be responders than those without. This has since been replicated with the SSRI fluoxetine (Bruder et al. 1996, 2004), and the NDRI bupropion (Bruder et al. 2007). Unfortunately, studies linking preferential response to antidepressant agents for MDD patients with a right-ear advantage have not been published to date.

**Molecular biology and immunology**

Although few such studies have been published to date, there is considerable potential for growth in this area. The results of an un-replicated study reported greater protein kinase A (PKA) activity from human skin cultured fibroblasts at baseline to predict a greater resolution of depressive symptoms following the treatment of MDD with an SSRI antidepressant (Shelton et al. 2005). Changes in phosphorylated cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB) concentrations were also found to correlate with symptom improvement in MDD in a separate study (Kock et al. 2002). In addition, the results of a more recent report also suggest higher post-treatment brain-derived neurotrophic factor (BDNF) levels among MDD patients who responded to treatment with the SSRI paroxetine or the SNRI milnacipran than treatment non-responders (Yoshimura et al. 2007), while two separate studies reported a positive correlation between symptom improvement and the degree of increase of BDNF levels in MDD (Gervasoni et al. 2005; Matrisiciano et al. 2009). However, the results of two subsequent studies did not report a significant correlation between BDNF levels at baseline or the change in BDNF levels during antidepressant treatment with symptom improvement (Hellweg et al. 2008; Huang et al. 2008).

S100B is a calcium-binding protein produced by astroglial cells that, at nanomolar concentrations, appears to promote neuronal growth while, at larger concentrations (micromolar), may promote apoptosis (Schroeter et al. 2002). Higher S100B levels immediately before treatment were found to predict a greater likelihood of clinical improvement following the treatment of MDD inpatients with either a SSRI or a TCA in one small study (Arolt et al. 2003). A subsequent meta-analysis (Schroeter et al. 2008) of three studies (Hetzel et al. 2005; Schroeter et al. 2002, 2008) confirmed a significant correlation between a reduction in S100B levels and a reduction in depressive symptoms among MDD patients during antidepressant therapy.

Finally, the results of one study suggest that lower interleukin-6 (IL-6) levels predict a greater probability of symptom resolution in MDD (Lanquillon et al. 2000), while the results of two studies have identified a correlation between reductions in tumour necrosis factor-alpha (TNF-α) levels and symptom improvement in MDD following antidepressant treatment (Eller et al. 2008; Lanquillon et al. 2000).

**Summary and conclusion**

A number of clinical predictors of efficacy for MDD have been identified to date, mostly from reports focusing on treatment with a SSRI including greater episode severity, the presence of Axis-I (especially anxiety disorders), or Axis-III (especially cardiovascular illness, hypofolataemia) comorbidity (these are associated with poorer outcome). The presence of one or more of these factors should alert clinicians to tailor their treatment approach in order to help maximize the chances of remission. Options for such patients may include initiating therapy with two treatments simultaneously, i.e. an antidepressant plus cognitive behavioural therapy (CBT) or interpersonal therapy (IPT), schedule more frequent follow-up visits, or resort to various next-step treatment strategies earlier for treatment non-responders (Papakostas, 2009). Several ‘leads’ have emerged of potential clinical mediators of efficacy including the presence of...
severe depression (showing an advantage for escitalopram, venlafaxine and duloxetine vs. ‘older’ SSRIs), anxious depression (showing a disadvantage for the NDRI bupropion vs. a SSRI), atypical depression (showing an advantage for a MAOI vs. a TCA), and hormonal status among women (showing an advantage for the SNRI venlafaxine vs. ‘older’ SSRIs). However, such ‘leads’ are, at best, preliminary and require replication. Finally, a number of studies have also identified a number of putative surrogate markers, either relating to serum-based (PKA, CREB, BDNF, S100B, IL-6, TNF-α), genetic (whether monoamine- or non-monoamine-related) or neurophysiologically based measurements as well as measures of prefrontal cortical metabolism, which appear to correlate with symptom improvement during the treatment of MDD with standard antidepressants. Although too few and far between to help provide a comprehensive understanding of the exact ‘downstream’ effects of a therapeutic agent which contributes to symptom resolution, conducting additional studies designed to establish reliable, replicable, and robust surrogate markers of efficacy in MDD could benefit the field in several ways, from enhancing our ability to develop more effective treatments to improving our ability to tailor a treatment for each individual patient designed to enhance outcome.

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Statement of Interest

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