On ‘polypharmacy’ and multi-target agents, complementary strategies for improving the treatment of depression: a comparative appraisal

Mark J. Millan
Unité du Recherche et Découverte en Neurosciences, Institut de Recherches Servier, Croissy sur Seine, Paris, France

Abstract
Major depression is a heterogeneous disorder, both in terms of symptoms, ranging from anhedonia to cognitive impairment, and in terms of pathogenesis, with many interacting genetic, epigenetic, developmental and environmental causes. Accordingly, it seems unlikely that depressive states could be fully controlled by a drug possessing one discrete mechanism of action and, in the wake of disappointing results with several classes of highly selective agent, multi-modal treatment concepts are attracting attention. As concerns pharmacotherapy, there are essentially two core strategies. First, multi-target antidepressants that act via two or more complementary mechanisms and, second, polypharmacy, which refers to co-administration of two distinct drugs, usually in separate pills. Both multi-target agents and polypharmacy ideally couple a therapeutically unexploited action to a clinically established mechanism in order to enhance efficacy, moderate side-effects, accelerate onset of action and treat a broader range of symptoms. The melatonin MT1/MT2 agonist and 5-HT2C antagonist, agomelatine, which is effective in the short- and long-term treatment of depression, exemplifies the former approach, while evidence-based polypharmacy is illustrated by the adjunctive use of second-generation antipsychotics with serotonin reuptake inhibitors for treatment of resistant depression. Histone acetylation and methylation, ghrelin signalling, inflammatory modulators, metabotropic glutamate-7 receptors and trace amine-associated-1 receptors comprise attractive substrates for new multi-target and polypharmaceutical strategies. The present article outlines the rationale underpinning multi-modal approaches for treating depression, and critically compares and contrasts the pros and cons of established and potentially novel multi-target vs. polypharmaceutical treatments. On balance, the former appear the most promising for the elaboration, development and clinical implementation of innovative concepts for the more effective management of depression.

Key words: Depression, epigenetic, histone, multi-functional, trace amine, treatment-resistance.

Introduction
Psychiatric disorders are generally characterized by a broad range of symptoms and high co-morbidity with other conditions, and they can be attributed to a diverse palette of neurochemical and structural dysfunctions provoked in turn by multifarious genetic, developmental, environmental and epigenetic factors.

In light of their multi-factorial origins and complex clinical profiles, it seems unlikely that disorders such as major depression and schizophrenia could be fully controlled in all patients by a drug possessing one single mechanism of action. This point is of considerable significance since the last decade has been dominated by the search for highly selective agents acting at a single target hypothesized to play a key role in the induction and/or control of specific disorders. Unfortunately, despite often compelling preclinical data, many selective agents have yielded mitigated results in clinical trials and not been progressed to authorization. This is not to say, however, that the target in question is necessarily irrelevant or inactive and,
apart from the use of selective drugs in subpopulations of patients and/or against certain subsets of symptoms, many targets might be more effectively exploited in association with other mechanisms of therapeutic activity. As outlined in this article, there are essentially two ways of achieving this goal with pharmacotherapeutics: polypharmacy (drug combinations); and multi-target drugs (several actions possessed by one drug).

In fact, the term ‘polypharmacy’ has something of an unfortunate reputation since it is sometimes practised in an unstandardized and ad hoc basis without formal supporting data, particularly in patients suffering from schizophrenia (Goodwin et al., 2009; Zink et al., 2010) and bipolar disorder (Lin et al., 2006; Goldberg et al., 2009). Counterproductively, the concomitant prescription of numerous drugs to certain psychiatrically ill patients – in particular the elderly, who typically take around six to eight – may compromise efficacy and provoke serious adverse drug reactions (Prudent et al., 2008). This type of polypharmacy is often associated with co-morbidity and generally encompasses a broad range of medication, including agents for controlling somatic complaints, as well as psychiatric and/or neurological problems (Mojtabai and Olsson, 2010). Major depression is also characterized by an increasing tendency for multiple drug use over the past decades, not only in geriatric populations but also in adults and the young (Glezer et al., 2009; Goodwin et al., 2009; McIntyre and Jerrell, 2009; Mojtabai and Olsson, 2010; Serna et al., 2010).

Conversely, the present article is concerned with the more positive dimension of evidence-based polypharmacy. That is, the controlled, validated and authorized use of drug combinations for improving antidepressant efficacy without any worsening of tolerance, in particular following guidelines in treatment-resistant patients who fail to respond adequately to monotherapy (Trivedi et al., 2006; Melander et al., 2008; Shelton et al., 2010; Connolly and Thase, 2011; Al-Harbi, 2012; Schlaepfer et al., 2012).

As regards drugs possessing multiple mechanisms of action, there has been a tendency to disparagingly consider them as ‘dirty’ and to accentuate the side-effects triggered by their ‘off-target’ actions. For example, the antimuscarinic, α1-adrenoceptor (AR) antagonist and histaminergic H1 antagonist properties of tricyclics (such as amitriptyline) and antipsychotics (such as clozapine) compromise cognition and elicit numerous autonomic and cardiovascular side-effects (Millan, 2006; Gillman, 2007; Sartorius et al., 2007). On the other hand, other components of their multi-target profiles – monoamine reuptake inhibition plus 5-HT2A antagonist properties for tricyclic antidepressants and dopamine (DA) D2/D3/5-HT2A antagonism plus 5-HT1A partial agonism for antipsychotics – accounts for their beneficial effects in treating depression and schizophrenia, respectively (Millan, 2006; Meltzer et al., 2012; Quesseveur et al., 2012).

Currently, there is particular interest in novel multimodal therapies that act at discrete subsets of targets mediating desirable actions while side-stepping mechanisms evoking undesirable side-effects. In this case, both polypharmacy (drug combinations) and multi-target agents are of potential interest and these strategies share a suite of therapeutic objectives, which, if fully realized, could markedly enhance the treatment and lives of patients suffering from depression (Table 1). The present article discusses the basic principles and the pros and cons of polypharmacy as compared to multi-target medication, evoking particular mechanisms that have been harnessed by both. It also considers a palette of innovative concepts under experimental exploration, which may eventually lead to the availability of more effective multi-modal antidepressants. The focus on major depression seems particularly appropriate in light of the disturbing current trend to disengage from ‘R’ and ‘D’ in this therapeutic domain despite well-recognized problems of treatment-resistance and sub-optimal remission (Miller, 2010; Nutt and Goodwin, 2011).

**Major depression, a complex and heterogeneous clinical profile with multiple risk factors**

Major depression is characterized by the cardinal symptoms of depressed mood and anhedonia, coupled to a state of despair and hopelessness, severe fatigue and loss of concentration, suicidal ideation and, in extreme cases, actual attempts at suicide (Millan, 2006; Sartorius et al., 2007; Uher, 2011). In addition, it is accompanied by a broad spectrum of other symptoms. Some are seen in a majority of depressed individuals, such as cognitive impairment and anxiety, whereas others are seen in only a minority, such as psychotic episodes and pain (Fig. 1). Moreover, depression is commonly co-morbid with: (1) psychiatric conditions such as obsessive–compulsive disorder, generalized anxiety disorder and schizophrenia; (2) neurological disorders such as Parkinson’s disease, Alzheimer’s disease and chronic pain; (3) somatic diseases such as diabetes, osteoporosis and cardiovascular disease (Millan, 2006; Sartorius et al., 2007; McIntyre et al., 2012). While not every patient will display all symptoms, depression is clearly a heterogeneous disorder with a broad range of symptoms requiring treatment.
It is possible that a single anomaly, such as a genetic mutation, could ultimately trigger a broad range of symptoms, in particular if it occurred early in development – and perinatal trauma is indeed a risk factor for depression (Uher, 2011; Heim and Binder, 2012). However, although certain monogenic neurodevelopmental conditions are associated with a broad range of dysfunction affecting both the brain and other organs (Kramer and van Bokhoven, 2009; Millan, 2013; Sanchez-Mut et al., 2012), depression is a polygenic disorder (cumulative impact of many genes with minor effects) that can be triggered or aggravated by adverse environmental events occurring at essentially any time of life from conception and foetal development via infancy and puberty to adulthood and senescence (Fig. 2) (Millan, 2006; Lohoff, 2010; Uher, 2011). Interestingly, both genetic and environmental factors converge onto epigenetic mechanisms controlling gene expression, which include DNA methylation and post-transcriptional histone marking as well as the control of mRNA processing and translation by non-coding RNAs (Covington et al., 2010; Lohoff, 2010; Uher, 2011; Millan, 2013; Mouillet-Richard et al., 2012; Sun et al., 2012). This interplay of mechanisms favouring (and countering) depressed states leads to a complex pattern of neuroplastic signalling and structural anomalies, both within and between neurones, and impacting a diversity of neural networks in the frontal hippocampus, amygdala and other corticolimbic structures (Fig. 1; Millan 2006; Covington et al., 2010; Autry and Monteggia, 2012; Dumas and Voleti, 2012; Heim and Binder, 2012; Schloesser et al., 2012). Thus, the multifaceted symptomatology of depression is mirrored by a complex hierarchy of cellular (neuronal and glial) anomalies manifested across overarching cerebral regions. It is also important to note that certain pathological changes anticipate the appearance of unambiguous clinical symptoms and diagnosis (Millan, 2006; Heim and Binder, 2012; Duman and Voleti 2012).

The above observations have several important implications for treatment. First, since network shifts are not always reversible, treatment should be initiated as soon as possible – ideally preventatively, once robust biomarkers become available (Millan 2008; Schmidt et al., 2011; Uher, 2011). Second, as discussed herein, it is likely that multiple mechanisms will need to be harnessed for the broad-based control of depressed states across substantial populations of patients, questioning the wisdom of highly selective agents. Third, multi-modal therapies concern both agents designed to normalize a pathological process causing depression, as well as symptomatic interventions for relief of symptoms by the manipulation of ‘intact’, compensatory substrates not affected by depression per se.

**Genome-driven, rational drug discovery: a decade of selective antidepressants in perspective**

There is a multitude of (interrelated and non-exclusive) explanations for the limited progress seen over the last
few decades in the pharmacotherapy of depression. They relate to all dimensions of the ‘R and D’ process as well as to authorization of new medication, embracing preclinical, clinical, regulatory, intellectual property and commercial issues. Several important points may be highlighted: persistent question-marks over the pertinence of animal models of depression; poor experimental validation of novel targets; the relevance of tests for evaluating potential antidepressant activity; their translational dimension, whether comparable procedures can be undertaken in humans; lack of rigorous patient recruitment for clinical investigations, use of antiquated rating scales and a strikingly high response to placebo (the most common cause of failed trials); the need to show superiority of a new drug if not over placebo, then over another antidepressant; increasingly stringent safety concerns; limited patent life for new drugs, generic competition and the difficulty in rapidly negotiating a realistic level of reimbursement for novel drugs from national institutions post-launch, in particular bearing in mind the comparatively low rate of success, yet high cost of development for central nervous system (CNS) drugs vs. other therapeutic areas (Brady et al., 2009; Miller, 2010; Nutt and Goodwin, 2011).

Three additional and interlinked issues that have dominated the agenda over the last decade should be briefly discussed since they are highly relevant to the development and use (or non-use) of multi-target drugs and polypharmacy. First, the impact of genomics and ‘rational’ drug discovery (Fig. 3); second, the above-mentioned preoccupation with highly-selective agents; third, the prioritization of novel, non-monoaminergic targets – with a particular focus on intracellular substrates of plasticity (Millan, 2006, 2008; Covington et al., 2010; Duman and Voleti, 2012; Autry and Monteggia, 2012; Connolly and Thase, 2012; Schloesser et al., 2012). It was originally thought

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**Fig. 1.** Symptoms other than depressed mood commonly associated with major depression. In addition to depressed mood and anhedonia, which are cardinal symptoms of major depression, it is often accompanied by a broad palette of other symptoms contributing to functional impairment. As outlined in the text, depression is also frequently co-morbid with a wide range of other central nervous system and somatic diseases, such generalized anxiety disorder and schizophrenia, Parkinson’s and Alzheimer’s disease, diabetes and cardiovascular disease. The complex pattern of symptoms and co-morbidity implies the involvement of numerous pathological processes and supports arguments in favour of treatments acting via several, complementary mechanisms of action.
that cloning the human genome would yield a significant number of new genes with novel functions, permitting a clarification of the causes of CNS dysfunction in psychiatric disorders and offering innovative targets for improved therapy. With hindsight, this proved naive. The number of protein-coding genes (about 21,000, or 3% of the genome) in humans scarcely differs from many ‘simpler species’ and complexity is derived more from epigenetic and other modes of transcriptional control, including regulatory and structural roles of many classes of protein non-coding RNA, and the operation of genes in networks (Millan, 2006; Cardon et al., 2009; Manolio et al., 2009; Penrod et al., 2011). Moreover, studies of the human genome have not yet led to any radically new insights into the causes of depression nor unveiled a palette of new sites for its treatment. Further, although it was anticipated that combinatorial chemistry and high-throughput screening would ‘revolutionize’ the detection of innovative drugs at established and novel targets (the ‘magic of high numbers’), this did not materialize, not least since the procedures used were rather simplistic and mainly aimed at identification of highly selective ligands (Brady et al., 2009; Campbell, 2010). In addition, despite impressive conceptual foundations and extensive experimental data, many selective antidepressants advanced into patients failed to demonstrate efficacy sufficient for registration (Millan, 2006, 2009; Miller, 2010). Finally, reflecting an understandable desire to explore novel therapeutic mechanisms, monoaminergic substrates were largely neglected (‘from monoamines to genomics’) despite the fact that there remained (and still remains) scope for their potentially more effective exploitation when coupled to other, non-monoaminergic sites (see below).
Ironically, then, the disavowal of monoaminergic mechanisms as obsolete in the search for improved treatment was not followed by the anticipated emergence of novel drugs aimed at hitherto unknown ‘genomic’ targets, but rather by a frustrating succession of inconclusive clinical trials with selective ligands acting at non-monoaminergic sites, such as neurokinin1 (NK1) and corticotrophin releasing factor (CRF1) receptors (Quartara et al., 2009; Kehne and Cain, 2010). This led to the inference that these mechanisms might actually be red herrings generated by misleading preclinical observations. However, these therapeutic trials were performed in far more challenging circumstances (not least, a high response to placebo) than predecessor substances such as selective inhibitors of 5-HT reuptake (SSRIs) and the assumption of a lack of clinical relevance may be an over-interpretation. The conviction remains that NK1 receptors, CRF1 receptors and certain other targets unsuccessfully evaluated in the clinic, as well as targets where clinical data are awaited, such as metabotropic glutamate (mGluR) 2 receptors (Bespalov et al., 2008; Campo et al., 2011), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Farley et al., 2010; Nations et al., 2012) and 5-HT7 receptors (Mnie-Filali et al., 2011), may well be of therapeutic relevance. However, they will best be exploited in a more effective multi-modal manner for the treatment of depression; that is, either in association with ‘alternative’ (non-medication) treatments or integrated with complementary mechanisms in polypharmacy and multi-target drugs (Fig. 4).

In addition to negative findings with highly selective agents in clinical trials, several arguments support the assertion that multi-modal pharmacotherapy may be more effective. First, despite their improved tolerance, SSRIs are no more effective than tricyclic agents. While 5-HT/noradrenaline (NA) reuptake inhibitors

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**Fig. 3.** The rational and reality of drug discovery for improved antidepressant (antidep) agents. Upon sequencing of the human genome, it was hoped that its ‘mining’ would rapidly identify many new potential targets for treating depression and other poorly controlled disorders. Unfortunately, as outlined in Figs. 1 and 2, depression is complex both as regards its causes and its characteristics, so the simplistic idea of finding a dysfunctional gene [by, for example, single nucleotide polymorphism (SNP) studies in man and gene knock-out (KO) techniques in mice] has proven elusive. Moreover, much of the genomic signal can be overwritten by epigenetic processes, many genes reciprocally interact with others to modify their mutual effects (epistasis), many have several functions – both favourable and detrimental – and gene functions are in general hard to establish. In addition, many genes were locked up in patents at the time of cloning the genome so ironically lost to research. Finally, ‘rational’ drug discovery based on high throughput screening (HTS) techniques coupled to combinatorial chemistry did not prove very effective in the search for leads for clinically effective antideps. The ‘reality’ is that genome-driven rational drug discovery remains very challenging, time-consuming and expensive, just like other modes of drug discovery.
appear to globally be more effective than SSRIs (with the possible exception of escitalopram – see below), tricyclics are still recognized as the most effective of antidepressants, likely reflecting their interaction not only with 5-HT and/or NA transporters, but also other sites such as 5-HT2A, 5-HT3C, 5-HT3B, 5-HT4, and α2-ARs. Furthermore, they exert a broad pattern of effects across various cerebral loci (Millan, 2006; Gillman, 2007; Sartorius et al., 2007; Cipriani et al., 2009). Second, antidepressant augmentation strategies are not simply a case of more of the same, but rather something else on top; that is, the incorporation of additional, mechanistically distinct actions. For tricyclics themselves, efficacy can be reinforced by adjunctive treatment with lithium or (although seldom employed) the thyroid hormones, triiodothyronine and thyroxine, while second generation antipsychotics such as aripiprazole, quetiapine and olanzapine amplify the efficacy of SSRIs, reflecting their interaction with a variety of other cellular substrates (McIntyre and Moral, 2006; Crossley and Bauer, 2007; Connolly and Thase, 2011; Al-Harbi, 2012). Other mechanisms of SSRI potentiation likewise act at sites very different from 5-HT transporters – see below. Third, both preclinical and clinical evidence suggests that electroconvulsive therapy as well as deep-brain and transcranial stimulation techniques for treatment of medication-refractory depression act via recruitment of broad-based neural circuits and multiple cellular and neurochemical substrates. Although fewer mechanistic data are available, the same seems to hold for sleep deprivation, which is rapidly effective in the relief of depressed states (Eitan and Lerer, 2006; Millan, 2006; Hemmeter et al., 2010; Bunney and Bunney, 2012; Del’Osso et al., 2012; Lee et al., 2012; Minichino et al., 2012).

While multi-target strategies are primarily conceived for promoting efficacy and accelerating onset of efficacy, they may even be better tolerated (Table 1). In this regard, older tricyclics display interactions at sites other than those mediating positive actions (see above), but the goal is to build what has
been termed ‘selectively non-selective’ agents directed against a chosen palette of targets transducing beneficial properties while eliminating interactions with sites eliciting side-effects (Hopkins et al., 2006; Millan, 2006; Morphy and Rankovic, 2006, 2007; Zimmermann et al., 2007; Wong et al., 2010; Peters et al., 2012). Thus, although the risk of additional side-effects should not be ignored, judiciously designed multimodal strategies may even possess improved tolerance. This is illustrated by antipsychotics possessing α2-AR and/or 5-HT2A antagonist properties to blunt induction of extrapyramidal actions and by the introduction of 5-HT2C antagonist properties into antidepressants to oppose side-effects of excessive 5-HT, such as sexual dysfunction and nervousness at the onset of treatment (Dekeyne et al., 2000, 2012; Millan, 2006; Meltzer et al., 2012).

Finally, as summarized in Table 1 and exhaustively discussed elsewhere (Millan, 2006), multi-modal treatments with complementary mechanisms of action should afford additional scope for the control of a greater range of symptoms accompanying depression (Fig. 1) and for the more effective alleviation of depression co-morbid with other conditions, such as anxiety disorders or Parkinson’s disease.

**Complementary mechanisms of antidepressant action: polypharmacy and multi-target exploitation**

It remains unclear to what extent the combination of established antidepressants at effective doses will guarantee a better patient response and, in certain cases, a lack of further improvement may reflect redundancy in the neuronal substrates mediating their actions (Millan, 2006; Blier et al., 2010; Bobo et al., 2011; Connolly and Thase, 2011; Rush et al., 2011; Al-Harbi, 2012; Rocha et al., 2012). Although there are examples where remission is indeed augmented, the most appealing feature of multi-modal strategies is the generation of novel antidepressant mechanisms that cannot otherwise be reproduced by the use of existing agents.

Melatonin MT1/MT2 receptors have attracted much interest in recent years in view of their role in controlling sleep and circadian rhythms, which are often perturbed in depression (Bunney and Potkin, 2008). The most compelling example of an innovative multi-target agent is currently agomelatine, a melatonin MT1/MT2 agonist and 5-HT2C antagonist, which has been clinically shown to relieve depressed states upon both short and long-term administration, and which also possesses anxiolytic properties (De Bodinat et al., 2010; Kasper et al., 2010; Srinivasan et al., 2011; Catena-Dell’Osso et al., 2012; Stein et al., 2012). Inasmuch as melatonin is ineffective alone in the relief of depression and selective 5-HT2C antagonists are unavailable for therapeutic exploration, this profile is unique and cannot be mimicked by polypharmacy. Nonetheless, motivated by studies of enhanced neurogenesis in rodents, a mixture of melatonin and buspirone (a 5-HT1A partial agonist) is in development and recently yielded positive findings in a controlled trial (Fava et al., 2012).

In contrast to agomelatine, as depicted in Table 2, the majority of multi-modal concepts for improving treatment of depression have been articulated around inhibition of 5-HT reuptake. That is, in the case of polypharmacy, adjunctive administration with SSRIs of a second agent with a contrasting mechanism of action and, as regards multi-target agents, the coupling to 5-HT reuptake inhibition of a further and different pharmacological action. While the diversity of ideas under experimental and/or clinical exploration cannot be comprehensively discussed herein (Millan, 2006, 2009; Butler and Meegan, 2008; Carvalho et al., 2008; Shelton et al., 2010; Wong et al., 2010; Schlaepfer et al., 2012; Al-Harbi, 2012; Connolly and Thase, 2012), the following observations are of particular interest within the framework of comparisons between multi-target and polypharmaceutical strategies.

Several monoaminergic (‘SSRI-plus’) strategies have been based around suppressing reuptake of NA and/or DA as well as 5-HT, blocking the negative feedback of monoamines at presynaptic sites inhibitory to release and/or blocking 5-HT2C receptors which, via recruitment of GABAergic interneurons, restrain monoaminergic transmission (Millan et al., 2000a, b, 2009; Millan, 2006; Sartorius et al., 2007). In principle, these goals can be attained by either drug association or by the use of equivalent multi-target drugs. Currently, 5-HT/NA reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine are generally considered somewhat more effective than SSRIs (Montgomery et al., 2007; Cipriani et al., 2009; Papakostas, 2010). One exception may be the ‘SSRI’, escitalopram, possibly reflecting its distinctive actions at allosteric sites on 5-HT transporters as well as its binding to a high affinity site on NA transporters (Nguyen et al., 2013; Plenge et al., 2012; Zhong et al., 2012). Not surprisingly, SNRIs are prescribed in preference to the association of a NA reuptake inhibitor with a SSRI. The DA reuptake inhibitor, buspirone, appears to be beneficial on top of SSRIs (Trivedi et al., 2006; Connolly and Thase, 2011) but, rather than dual-acting drugs recognizing 5-HT and DA transporters, there has been considerable interest in triple monoamine reuptake inhibitors – although
### Table 2. Strategies for enhancement of SSRI efficacy based upon augmentation with a complementary mechanism of action, either as pharmacotherapy or as an equivalent multi-target agent

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Primary neuronal substrates</th>
<th>Potential advantages</th>
<th>Potential disadvantages</th>
<th>Clinically tested agents</th>
<th>Multi-target equivalent</th>
<th>References</th>
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<tbody>
<tr>
<td>NA reuptake inhibition</td>
<td>†NA ext †DA ext (FCX)</td>
<td>†Delay †Motor retardation</td>
<td>CV side-effects</td>
<td>Reboxetine Desipramine (†efficacy)</td>
<td>Venlafaxine&lt;sup&gt;1&lt;/sup&gt; Duloxetine&lt;sup&gt;1&lt;/sup&gt; Desvenlafaxine&lt;sup&gt;2&lt;/sup&gt; Milnacipran&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Millan et al., 2001a, b; Lopez-Munoz et al., 2007; Sarriouris et al., 2007</td>
</tr>
<tr>
<td>DA/NA reuptake inhibition</td>
<td>†NA ext †DA ext</td>
<td>†Delay †Motor retardation</td>
<td>CV tolerance</td>
<td>Bupropion (†efficacy)</td>
<td>Amitifadine II Tesofensine, II&lt;sup&gt;10&lt;/sup&gt; JNJ-725476&lt;sup&gt;1c&lt;/sup&gt; JZAD-JV-22&lt;sup&gt;1c&lt;/sup&gt;</td>
<td>Trivedi et al., 2006; Aluisio et al., 2008; Calderone et al., 2010; Tran et al., 2012</td>
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<td>5-HT&lt;sub&gt;1A&lt;/sub&gt; antagonist (autoreceptor)</td>
<td>†5-HT ext †ACh ext (FCX, hippocampus)</td>
<td>†Delay †Cognition †Sleep (Alzheimer's disease)</td>
<td>Interference with post-synaptic antidepressant properties.</td>
<td>(-)-Pindolol (variable †efficacy/†delay)</td>
<td>SB649,915&lt;sup&gt;PC&lt;/sup&gt; WAY-211,612&lt;sup&gt;PC&lt;/sup&gt;</td>
<td>Starr et al., 2007; Watson and Dawson, 2007; Beyer et al., 2012</td>
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<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;/1B antagonist (autoreceptor)</td>
<td>†NA ext †DA ext (FCX) †ACh (FCX, hippocampus)</td>
<td>†Anxiety †Cognition †Sexual dysfunction (GAD)</td>
<td>Poor tolerance Nausea Nervousness</td>
<td>Buspirone (little †efficacy)</td>
<td>Vilazodone&lt;sup&gt;1&lt;/sup&gt; OPC14525&lt;sup&gt;PC&lt;/sup&gt;</td>
<td>Dawson and Bromidge, 2007; De Paulis, 2007; Frampton, 2011</td>
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<tr>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt; antagonist</td>
<td>†NA/DA ext (FCX, hippocampus)</td>
<td>†Anxiety †Sexual dysfunction (control of stress responsive limbic circuits) †Sleep</td>
<td>Weight gain Motor stimulation</td>
<td>Ritanserin Mirtazapine (†efficacy)</td>
<td>Trazodone&lt;sup&gt;1&lt;/sup&gt; Lu-AA24530</td>
<td>Millan, 2005; Cremers et al., 2007; Blier et al., 2010</td>
</tr>
<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;-AR antagonist (autoreceptor)</td>
<td>†DA/ACh (FCX) †ACh (FCX, hippocampus)</td>
<td>†Cognition †Sexual dysfunction (Parkinson's disease)</td>
<td>CV tolerance Endocrine side-effects</td>
<td>Yohimbine (†efficacy/†delay)</td>
<td>S35966&lt;sup&gt;PC&lt;/sup&gt; R226,161&lt;sup&gt;PC&lt;/sup&gt;</td>
<td>Cordi et al., 2001; Sanacora et al., 2004; Andres et al., 2007</td>
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<tr>
<td>Dopamine D&lt;sub&gt;2&lt;/sub&gt; agonist</td>
<td>Recruitment of mesolimbic reward systems</td>
<td>†Anhedonia †Reward (Parkinson's disease)</td>
<td>Nausea Abuse potential CV side-effects Psychosis</td>
<td>Pramipexole OPC34712 (†efficacy&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>WS-50030</td>
<td>Rogoz and Skuza, 2006; Brennan et al., 2010</td>
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<td>Histamine H&lt;sub&gt;3&lt;/sub&gt; antagonist</td>
<td>†Hist/ACh ext (FCX, hippocampus) †NA/DA ext (FCX)</td>
<td>†Cognition †Attention (Parkinson's, Alzheimer's disease, ESD, narcolepsy) †Wakefulness</td>
<td>Not described</td>
<td>Not described</td>
<td>JNJ-28583847&lt;sup&gt;PC&lt;/sup&gt;</td>
<td>Barbiere et al., 2007; Stocking et al., 2010</td>
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<td>Acetylcholinesterase inhibitor</td>
<td>†ACh ext (†degradation)</td>
<td>†Cognition (Alzheimer’s disease)</td>
<td>Poor tolerance</td>
<td>Not described</td>
<td>RS-1259&lt;sup&gt;PC&lt;/sup&gt;</td>
<td>Abe et al., 2003</td>
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Table 2 (cont.)

<table>
<thead>
<tr>
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<tr>
<td>Nicotinic ((\alpha_4/\beta_2) and (\alpha_3/\beta_4&gt;\alpha_7)) antagonist</td>
<td>Limbic actions: precise neuronal substrates unclear</td>
<td>↓Delay</td>
<td>Unclear</td>
<td>(S)-Mecamylamine (TC-5224), IIID (variable ↑efficacy)</td>
<td>Not described</td>
<td>George et al., 2008; Bacher et al., 2009; Philip et al., 2012</td>
</tr>
<tr>
<td>AMPA positive allosteric modulator</td>
<td>↑BDNF and ↑Neurogenesis ↑Neural plasticity</td>
<td>↑Cognition ↑Attention</td>
<td>Overstimulation in presence of high glutamate levels?</td>
<td>Not described</td>
<td>LY392,098PC</td>
<td>Li et al., 2003; Farley et al., 2010; Nations et al., 2012</td>
</tr>
<tr>
<td>NMDA channel blocker</td>
<td>↑5-HT/DA ext ↑BDNF and ↑mTOR/↑GSK-3β ↑AMPA signalling</td>
<td>↑Neurotoxic damage ↑Delay (Parkinson’s disease)</td>
<td>Psychosis Motor disruption Cognitive deficits</td>
<td>AZD6765 (Efficacy study underway)</td>
<td>Not described</td>
<td>Aan het Rot et al., 2012; Bunney and Bunney, 2012; Ibrahim et al., 2012; Zarate et al., 2013</td>
</tr>
<tr>
<td>Neurokinin1 antagonist</td>
<td>↑5-HT ext (FCX, hipp) ↑NA/DA (FCX) ↑BDNF</td>
<td>↓Delay ↓Anxiety ↓Pain and nausea (GAD, OCD)</td>
<td>Unclear</td>
<td>Vestipitant, IIID Results not disclosed</td>
<td>GSK424,887PC</td>
<td>Gobert et al., 2008; Millan et al., 2010; Quartara et al. 2009; Ratti et al., 2011</td>
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<tr>
<td>CRF1 antagonist</td>
<td>↓HPA overdrive and limbic over-activation in response to stress</td>
<td>↓Anxiety ↓Stress ↓Inflammation (GAD, inflammatory bowel disorder)</td>
<td>↓Basal corticosterone release</td>
<td>(R121,919, IIID, GR561,679,IIID) Interaction studies probably not done?</td>
<td>Several patents</td>
<td>Millan, 2009; Kehne and Cain, 2010</td>
</tr>
<tr>
<td>Glucocorticoid antagonist/synthesis inhibitor</td>
<td>↓Neurotoxic and ‘amnesic’ actions of excess stress corticosterone. ↑AMPA expression ↑NA/5-HT ext. ↑Pro-inflammatory mediators like IL6</td>
<td>Neuroprotective ↑Psychosis ↑Cognition</td>
<td>↓Baseline HPA activity. Not desirable for atypical/seasonal depression</td>
<td>Mifepristone, IIID Metapyrone, IIID (variable ↑efficacy)</td>
<td>Not described?</td>
<td>Shatzberg and Lindley, 2006; Gallagher et al., 2008</td>
</tr>
<tr>
<td>COX 2 inhibition*</td>
<td>↑NA/5-HT ext. ↑Pro-inflammatory mediators like IL6</td>
<td>Anti-inflammatory Analgesic. Adjunctive treatment of schizophrenia?</td>
<td>Gastrointestinal side-effects. ↑Risk heart attacks and stroke (?).</td>
<td>Celecoxib Naproxen</td>
<td>Not described</td>
<td>Müller et al., 2006, 2010; Abbasi et al., 2012; Johansson et al., 2012</td>
</tr>
<tr>
<td>Melanocortin 4 agonist</td>
<td>↓Stress-induced activation of HPA, limbic actions</td>
<td>Metabolic, CV and endocrine side-effects</td>
<td>Not evaluated</td>
<td>MCL-0042PC</td>
<td>Not described</td>
<td>Chaki et al., 2005; Chaki and Okubo, 2007</td>
</tr>
<tr>
<td>Oestrogen receptor (\beta) agonist</td>
<td>↑NA/5-HT ext. Modulation GABA transmission. P21-kinase and ERK recruitment.</td>
<td>Metabolic, CV and endocrine side-effects</td>
<td>Not described</td>
<td>MCL-0042PC</td>
<td>Not described</td>
<td>Hughes et al., 2008; Molinda-Hernandez and Tellez-Alcantara 2011</td>
</tr>
</tbody>
</table>
Quetiapine

Weight gain

L, CV, metabolic, motor (akathisia) side-effects

Anxiety

Not described Goodwin et al., 2007; Carvalho et al., 2008; Connolly and Thase, 2011

Second generation antipsychotics (schizophrenia, OCD, GAD) possibly glutamate (FCX)

Aripiprazole (5-HT2A/2C antagonist, DA, Dopamine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; PC, preclinical; L, launched (approved); D, discontinued (note, actual drug status not always obvious); CV, cardiovascular; EDSD, excessive daytime sleep disorder; HPA, hypothalamo-pituitary axis; COX 2, cyclooxygenase-2; PAG, partial agonist.

* Celecoxib also tested in association with the noradrenaline (NA) reuptake inhibitor, reboxetine. Olanzapine has only been tested in association with fluoxetine (Symbax®).

Lu-AA24530 is also a 5-HT3 antagonist.

This is not an exhaustive inventory of all drugs to date tested in association with antidepressants, nor a compendium of every multi-target evaluated in experimental models of depression. Rather, for polypharmacy, it focuses on association with selective serotonin reuptake inhibitors (SSRIs) ... table depicts comparable SRI-based multi-target concepts where experimental data suggest that the mechanism presents benefits vs. 5-HT reuptake inhibition alone. In certain cases, no comparable multi-target agent has been described. Further, in most cases – although experimental (ex vivo) monomolecular agents are depicted, some mechanisms are especially promising for accelerating onset. For further information see Carvalho et al., 2006; Millan, 2006, 2009; Shelton et al., 2010; Connolly and Thase, 2011, 2012; Schlaepfer et al., 2012).

In an effort to mimic the 5-HT1A (dendritic) and 5-HT1B (terminal) autoreceptor desensitization thought to underlie the progressive onset of antidepressant efficacy for SSRIs, both polypharmaceutical and multi-drug pistes have been pursued. However, despite a plethora of preclinical findings and promising clinical evidence for an accelerated onset of action, gains in efficacy have proven inconsistent upon co-administration of the 5-HT1A antagonist, (−)-pindolol, with SSRIs (Artigas et al., 2006; Dawson and Bromidge, 2008; Connolly and Thase, 2012). This may reflect its residual intrinsic efficacy at autoreceptors and, by analogy, it has proven difficult to link pure antagonist properties at 5-HT1A and/or autoreceptors to suppression of 5-HT reuptake, although several mixed ligands have now been documented (Millan, 2006, 2009; Starr et al., 2007; Watson and Dawson, 2007; Beyer et al., 2009). Rather paradoxically, then, notwithstanding: (1) studies in rats indicating that 5-HT1A partial agonists blunt SSRI-induced increases in 5-HT levels (Gobert et al., 1999); (2) less than scintillating findings with adjunctive use of the 5-HT1A partial agonist, buspirone, in depression (Millan, 2006; Connolly and Thase, 2011), it is the mixed 5-HT1A partial agonist/SSRI, vilazodone, that has been granted approval for treatment of depression (De Paulis, 2007; Dawson and Bromidge, 2008; Reed et al., 2012). Rather than 5-HT, alterations in levels of other transmitters such as acetylcholine, NA and DA may account for any potential advantages of vilazodone over SSRIs (Millan et al., 1994; Millan, 2006; Watson and Dawson, 2007).

While partial agonism at 5-HT1A receptors favours NA and DA release in the frontal cortex (Millan et al., 2000a, b), their elevation can be more robustly and reproducibly achieved by blockade of 5-HT1C receptors. The induction of NA and DA release marries well with inhibition of 5-HT reuptake and 5-HT1C antagonism affords additional anxiolytic and sleep-enhancing properties while opposing the sexual dysfunction provoked by excessive levels of 5-HT (Dekeyne et al., 2000, 2008; Millan, 2005; Quesseveur et al., 2012). 5-HT1C antagonism is inherent to many tricyclic agents as well as to trazodone (of which a new long-release form is becoming available), but these drugs all have other undesirable actions like histamine H1 receptor and α1-AR blockade (Millan, 2006; Gillman, 2007; Stahl, 2009). Hence, dual 5-HT1C antagonists/SSRIs shorn of detrimental actions still appear attractive;
in particular, since selective 5-HT\textsubscript{2C} antagonists for association with SSRIIs are not clinically available and since mirtazapine, which potentiates the actions of SSRIs, shares the potent H1 and \(\alpha_1\)-AR antagonist actions of tricyclics (Blier et al., 2010; Connolly and Thase, 2011; Watanabe et al., 2011). More favourably, mirtazapine antagonizes \(\alpha_2\)-ARs inhibitory to monoaminergic transmission and, mirroring preclinical work, clinical data suggest that \(\alpha_2\)-AR blockade hastens and intensifies antidepressant properties elicited by monoamine reuptake inhibition (Sanacora et al., 2004). Correspondingly, mixed \(\alpha_2\)-AR/SSRIs and \(\alpha_2\)-AR/SNRIs, in which negative feedback at \(\alpha_2\)-ARs autoreceptors is interrupted, display powerful antidepressant profiles in rodents (Cordi et al., 2001; Andres et al., 2007; Millan, 2009; Serres et al., 2012).

It is frustrating that these agents have not been authorized for the control of treatment-resistant depression, primarily due to concerns of untoward cardiovascular side-effects. Inasmuch as the above lines evoked the interest of associating 5-HT\textsubscript{2C} and \(\alpha_2\)-AR antagonism with SSRIIs, it is possible that dual 5-HT\textsubscript{2C}/\(\alpha_2\)-AR antagonists lacking the potential side-effects of mirtazapine were recently described, although their clinical effects await characterization (Dekeyne et al., 2012; Millan et al., 2012).

All the above-evoked monoaminergic strategies would be expected to reinforce dopaminergic transmission in the frontal cortex and hence to counter depressed mood and impairment of cognitive domains such as executive function and working memory, but only triple reuptake inhibitors should elevate extracellular levels of DA in limbic structures (Millan et al., 2000a, b, 2012; Skolnick and Basile, 2006; Alusiso et al., 2008; Millan, 2009; Tran et al., 2012). Mesolimbic actions counter both motor retardation and depressive mechanisms of reward, of particular relevance to melancholic depression and depression co-morbid with Parkinson’s disease. An alternative approach would be to directly recruit post-synaptic D\textsubscript{2} receptors by use of drugs possessing agonist properties and both polypharmaceutical and multi-target approaches have been described in this regard but, perhaps in view of numerous issues of tolerance, little real progress has been made and this line of research does not appear particularly inspiring (Rogoz and Skuza, 2006; Brennan et al., 2010; Al-Harbi, 2012). Positive phase II efficacy studies associating the nicotinic antagonist, (S)-mecamylamine, with SSRIs led to much excitement, but more recent phase III investigations were something of an anti-climax, leading to termination of its development in depression. The precise reasons underlying inadequate and/or inconsistent clinical efficacy remain to be elucidated, but it is worth noting evidence that both blockade and/or stimulation of \(\alpha_2\)-\(\beta_2\) nicotinic sites in rodents positively influences depressed mood in rodents, while the molecular substrates for putative antidepressant actions of (S)-mecamylamine warrant further investigation (Millan, 2006; George et al., 2008; Bacher et al., 2009; Andreasen et al., 2011; Philip et al., 2012). Regrettably, although there is considerable cross-talk amongst nicotinic ligands (certain of which interact with 5-HT transporters) and SSRIs (several of which recognize nicotinic receptor subtypes, Millan, 2006), these structure-activity insights do not appear to have systematically exploited for generation of multi-target nicotinic agents of potentially more robust antidepressant efficacy than either class of agent alone – or, indeed, their combination.

Another mechanism worth highlighting is \(N\)-methyl-D-aspartate (NMDA) receptor blockade inasmuch as a suite of recent studies has shown that the NMDA receptor channel blocker, ketamine, at subanaesthetic doses, elicits robust and rapid antidepressant properties (Aan Het Rot et al., 2012; Bunney and Bunnel, 2012). NMDA receptor antagonists are known to recruit frontocortical and subcortical monoaminergic pathways in rodents. In addition, AMPA receptors and the modulator of mRNA translation and neuroplasticity, mammalian target of rapamycin (mTOR) – which is deficient in depression (Jernigan et al., 2011) – are implicated in the actions of ketamine (Maeng et al., 2008; Li et al., 2010; Aan Het Rot et al., 2012). To date, the combined administration of ketamine with SSRIs has not been documented, but a clinical evaluation of this question is currently underway with a further, low affinity non-competitive antagonist at NMDA receptors, AZD6765 (Connolly and Thase, 2012). The integration of 5-HT transporter and NMDA channel blocking activity into a single drug seems unlikely but an alternative approach may be to combine SSRI activity with selective blockade of the NR2B receptor subunit in a single drug since: (1) NMDA receptors containing this subunit seem to be the major class involved in the control of mood and depressed states; (2) selective ligands at NR2B subunits are under evaluation for potential antidepressant properties in animals and man (Aan Het Rot et al., 2012; Ibrahim et al., 2012). The major concerns for the broader use of this concept, whether as drug combinations or multi-target agents, is the induction of psychosis and blunting of efficacy upon prolonged administration (Aan Het Rot et al., 2012; Mathew, 2012). In any event, the actions of ketamine may provide insights into molecular substrates permitting...
more rapid control of depression by other, more tractable strategies. Interestingly, mGluR2 antagonists, which likewise possess potential antidepressant properties, mimic ketamine in recruiting mTOR in the frontal cortex (Dwyer et al., 2012). Note, however, the caveat that: (1) NMDA receptor blockade is pro-psychotic; (2) mGluR2 receptors are deficient in schizophrenia and antagonists possess potential pro-psychotic properties (Nicoletti et al., 2011); while (3) over-expression of mTOR in the frontal cortex accounts for certain cognitive deficits of both schizophrenia and neurodevelopmental disorders like Fragile X (Meffre et al., 2012; Millan, 2013).

In view of the impressive pedigree of data supporting their roles in the response to stress, the control of mood and the induction of depressed states, two of the most conspicuous failures to achieve authorization (so far) are CRF1 and NK1 receptor antagonists (Quartara et al., 2009; Kehne and Cain, 2010; Ratti et al., 2011). As pointed out above, the core problem may be that these mechanisms are not sufficient for robust efficacy alone and require integration with other actions. While compounds inhibiting 5-HT transport and blocking CRF1 receptors are feasible and active in vivo (M.J. Millan, unpublished observations), appropriate pharmacokinetic parameters remain elusive. Rather oddly, the effects of co-administration of CRF1 antagonists and SSRIs in humans do not appear to have been investigated despite the inherent logic underpinning such studies, especially in psychotic depression and mixed depression/anxiety. Today, CRF1 antagonists are mainly being pursued for anxiety disorders and irritable bowel syndrome (Millan, 2009; Kehne and Cain, 2010). As for NK1 receptors, a high-profile report of antidepressant actions of the selective NK1 antagonist, aprepitant, had considerable resonance but these actions could not be consistently confirmed by succeeding studies, even at doses shown to saturate NK1 receptors – possibly due to an intervening amplification of the response to placebo in the course of clinical trials, rather than any ostensible loss of efficacy (Millan, 2009; Quartara et al., 2009; Ratti et al., 2011). Although this remains to be clarified, other selective NK1 antagonists have hardly fared better so they are now employed mainly for control of chemotherapy-evoked nausea and vomiting arising in the treatment of cancer – as part of a multi-drug treatment package designed to enhance efficacy (Ratti et al., 2011; Dos Santos et al., 2012). Mixed NK1 antagonists/SSRIs have been documented in preclinical studies, where they manifest the positive attributes of each of these class of compounds, and their profiles resemble those of combined injection of selective NK1 antagonists and SSRIs, although data from humans are awaited (Brocco et al., 2008; Gobert et al., 2009; Millan et al., 2010). Further, mirroring findings with concomitant administration of selective NK1 antagonists and SSRIs in rodents, vestipitant has been under development as polypharmacy with SSRIs for the treatment of major depression (Millan, 2009). To date, clinical data have not been disclosed, the status of this project is uncertain and it may have been abandoned for strategic reasons related to factors other than clinical efficacy. The theoretical and experimental arguments supporting co-joint blockade of NK1 receptors and 5-HT reuptake for treatment of depression are compelling. Both classes of drug are safe and well studied, so this still remains an ideal platform for a structured comparison of multi-target drugs vs. polypharmacy for the ameliorated treatment of depression.

Contrasting with NK1 antagonists, there is abundant support for the use of second-generation antipsychotics as adjuncts to SSRIs in the control of treatment-resistant depression and data are particularly solid for aripiprazole and olanzapine (both authorized), although the latter was evaluated only with fluoxetine (Connolly and Thase, 2011). The precise mechanisms involved in the potentiation of SSRI efficacy remain to be defined, but a role for partial agonist properties at 5-HT1A receptors, as well as blockade of 5-HT2A/2C receptors and α2-ARs seems probable. These mechanisms were evoked above and blockade of 5-HT7 sites may likewise be implicated inasmuch as their inactivation is associated with antidepressant properties in rodents – although clinical data for 5-HT7 antagonists alone and together with SSRIs are not yet available (Mnie-Filali et al., 2011). Partly in view of the complex pharmacological profiles of second-generation antipsychotics, but also in light of the robust results attained upon their association with SSRIs, there have been no real attempts to reproduce this profile with a multi-target strategy. Note that the major metabolite of quetiapine possesses affinity for NA transporters and ziprasidone for 5-HT transporters, suggesting that such multi-target compounds would be feasible from a chemical perspective (McIntyre et al., 2007; Millan, 2009).

Depressive states in humans and experimental models of depression in rodents are associated with inflammation and elevations in levels of interleukins. These observations have prompted studies of the potential adjunctive use of inhibitors of cyclooxygenase-2 like Celecoxib, both with SSRIs and with the NA reuptake inhibitor, reboxetine (Müller et al., 2006; Guo et al., 2009, 2009; Muller, 2010;
Capuron and Miller, 2011; Abbasi et al., 2012; Leonard and Maes, 2012). Despite promising data, and preclinical studies suggesting that Celecoxib acts both by anti-inflammatory mechanisms and via an influence on monoaminergic transmission (Muller, 2010; Johansson et al., 2012; Krause et al., 2012; Leonard and Maes, 2012), clinical observations remain limited. Further, not all data support benefits of associating anti-inflammatory agents with SSRIs (Warner-Schmidt et al., 2011). Accordingly, there is a need for further evaluation of this intriguing concept in patients, yet studies have – not unexpectedly – been restrained by questions concerning the cardiovascular safety of this class of drugs.

To date, no mixed SSRI/cyclooxygenase 2 inhibitors are known and, despite the above indications that many other classes of multi-target drug incorporating 5-HT reuptake can be designed, a number of augmentation mechanisms would be challenging to incorporate into a single chemical structure. For example, as regards the actions of thyroid hormones (triiodothyronine and thyroxine), inhibitors of corticosterone release and favour cognitive performance – have not been brought to fruition, even in patients showing psychotic depression, where the hypothalamic-pituitary axis activity is disinhibited (Millan, 2006; Gallagher et al., 2008; Schatzberg and Lindley, 2008; Molina-Hernandez and Tellez-Alcantara, 2011; Connolly and Thase, 2012). Note, however, that thyroid hormones are little used today and that data for oestrogen agonists (mostly tested in peri-menopausal women) remain preliminary. Moreover, despite considerable efforts and a strong rationale, clinical studies with mefenpristone (a glucocorticoid antagonist) and metyrapone (an inhibitor of glucocorticoid synthesis) – which should protect cells from detrimental effects of excessive stress-induced corticosterone release and favour cognitive performance – have not been brought to fruition, even in patients showing psychotic depression, where the hypothalamic-pituitary axis activity is disinhibited (Millan, 2006; Gallagher et al., 2008; Schatzberg and Lindley, 2008).

Other examples (not depicted in Table 2) of absent multi-target lookalikes for a clinically tested SSRI augmentation strategy include instances where the drug added on: (1) has a poorly defined mechanism; (2) acts itself in a multi-target fashion; (3) the association has yielded ambivalent experimental and clinical data providing only a modest incentive to launch a discovery programme for an equivalent multi-target agent. Anticonvulsants such as riluzole and lamotrigine illustrate this point, as does the ‘stimulant’ methylphenidate (Carvalho et al., 2008; Connolly and Thase, 2011, 2012). Another prominent example is modafinil (and its active isomer, armodafinil) which exerts a complex pattern of actions via monoaminergic, glutamatergic and orexinergic mechanisms. Modafinil revealed modest and possibly non-sustained improvements in mood upon addition to SSRIs and, not surprisingly in view of its wake-promoting characteristics, reduced fatigue (Minzenberg and Carter, 2008; Shelton et al., 2010; Connolly and Thase, 2012; Millan, 2013).

Finally, the most striking feature of Table 2 is just how few drug combinations and/or comparable multi-target agents have been formally authorized and become available to patients despite an abundance of auspicious preclinical data, compelling hypotheses and at least small-scale clinical testing. Clearly, there is considerable scope for further work to clinically validate these and other (see below) multi-modal concepts for the improved treatment of depression.

### Polypharmacy and multi-target agents: similarities and differences, advantages and disadvantages

As outlined above, theoretical considerations, experimental studies and, in several instances, clinical feedback underscores the interest of multi-modal treatment strategies for the improved treatment of depression, although much remains to be learned. While polypharmaceutical strategies and multi-target agents share certain features, they also reveal differences and both have their merits and their disadvantages, as summarized in Table 3.

The principal challenge with multi-target agents is the integration of two or more (preferably overlapping) pharmacophores into a small structure (molecular weight not more than 500 if possible) in order to reconcile chosen promiscuity with favourable pharmacokinetic properties of CNS penetration and biostability (Hopkins et al., 2006; Millan, 2006; Morphy and Rankovic, 2006, 2007; Zimmermann et al., 2007; Wong et al., 2010). Ironically, more than a decade of focus on highly selective ligands has enhanced the ability of chemists to eliminate (unwanted) activities rather than favour their integration when desired. Nonetheless, while structure–activity relationships for multi-target ligands can be challenging, it is not usually necessary to generate compounds with high affinities for two sites. As a rule, more modest affinities than for selective agents suffice and the real issue is acquiring an appropriate balance as defined less in vitro than by use of in vivo experimental models of depression (see above citations). This can be arduous and it is hard to be certain that the ratio of activities is optimal,
<table>
<thead>
<tr>
<th>Factor</th>
<th>Polypharmacy (drug combinations)</th>
<th>Multi-target agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>General acceptance</td>
<td>Non-evidence-based polypharmacy is discouraged for CNS disorders and especially problematic in the elderly. However, when mechanisms are supported by clinical data, administration is carefully monitored and drugs are prescribed in accordance with guidelines to poorly responsive patients, it is an important option.</td>
<td>No inherent difference in attitude to multi-target vs. selective agents for patients or prescribers, although the potential advantages of multi-target over highly selective agents are still insufficiently recognized.</td>
</tr>
<tr>
<td>Generation and design of drugs</td>
<td>If individual drugs exist, they can be combined, although there may be issues of intellectual property and availability. If drugs with desired pharmacological activities are inexistent, then combination is impossible. A mixture of more than three compounds is rarely a realistic proposition.</td>
<td>In principle, any hypothetical association of two or more actions can be built into one chemical structure. However, structure–activity relationships are more challenging and onerous than for selective agents and some may be chemically unrealizable.</td>
</tr>
<tr>
<td>Hypothesis validation, experimental evaluation</td>
<td>Characterization of drug combinations requires testing of components alone and in association, time-consuming for determination of optimal ratios, which may be test-symptom dependent. However, drug ratios can still be titrated in the clinic.</td>
<td>Once the hypothesis is validated, multi-target drugs can be characterized similarly to selective agents. However, the ratio of respective activities is invariant and cannot be adjusted in the clinic.</td>
</tr>
<tr>
<td>Therapeutic range and properties</td>
<td>Additional activities should expand therapeutic range, although they may also introduce constraints, e.g. dopamine D_{2} agonist properties are fine for Parkinson’s disease but unacceptable for psychotic depression.</td>
<td>Same potential advantages and limitations as for polypharmacy.</td>
</tr>
<tr>
<td>Tolerance, therapeutic window</td>
<td>Additional activities may bring other side-effects, yet tolerance can be improved. Thus, a second mechanism of additive or synergistic antidepressant activity allows for reduced doses of each at equivalent efficacy, hence enhancing the therapeutic window. Certain actions may directly counter side-effects, e.g. 5-HT_{2C} antagonism to counter sexual dysfunction and nervousness.</td>
<td>Same potential advantages and limitations as for polypharmacy.</td>
</tr>
<tr>
<td>Safety/toxicity testing</td>
<td>Toxicological and safety pharmacology profiles need to be available for both drugs separately as well as together.</td>
<td>Spared the drawback of polypharmacy, no disadvantage vs. selective agents.</td>
</tr>
<tr>
<td>Drug pharmacokinetics</td>
<td>Pharmacokinetic profiles (time to max. effect, half-life, etc.) of component drugs need to be comparable for co-administration to make sense.</td>
<td>Spared the drawback of polypharmacy, no disadvantage vs. selective agents.</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Drug interactions among component ligands need careful monitoring, such as those related to cytochrome 450 isomorph inhibition. Interactions with other drug classes especially complicated.</td>
<td>Spared the drawback of polypharmacy, no disadvantage vs. selective agents.</td>
</tr>
<tr>
<td>Clinical testing</td>
<td>Designs complex, both vs. placebo and vs. comparative agents. Large scale, long-term trials not easy, especially if other than add-on to SSRIs. Industry primarily interested in testing novel monotherapy*.</td>
<td>Spared the drawback of polypharmacy, no disadvantage vs. selective agents.</td>
</tr>
<tr>
<td>Compliance</td>
<td>Major issue for antidepressants: may be even more problematic for multiple pills although improved efficacy should favour adherence.</td>
<td>Spared the drawback of polypharmacy, no disadvantage vs. selective agents.</td>
</tr>
</tbody>
</table>
a core consideration since it is obviously invariant and cannot later be modified in the clinic.

Conversely, drug associations can be titrated in patients, with one component (like a SSRI) remaining constant and the other being systematically varied, although, for pragmatic reasons and in view of time and cost, a fairly well-defined notion of the desired drug:dose ratio should be available before commencing clinical studies. Moreover, as outlined in Table 3, in particular where the two drugs to be combined are not well characterized in humans, there are many developmental, pharmacokinetic and clinical issues that are more complex to address for drug combinations than for multi-target (or selective) agents. To date, most polypharmaceutical concepts have been limited to small-scale trials, where at least one drug is commercially available, and the concomitant development from scratch of two novel ligands in association has not, to the author’s knowledge, been accomplished. Indeed, while polypharmacy for depression is incarnated by the approval of adjunctive use of second-generation antipsychotics (such as aripiprazole) with SSRIs in treatment-resistant subjects, both of these drug classes are well known, of proven clinical utility and inherently ‘safe’. Further, olanzapine has been specifically developed in association with fluoxetine, both drugs emanating from the same company (Lilly). The development of drug mixtures containing two or more new chemical entities from the outset is a far more formidable challenge.

Polypharmacy and multi-target agents both have their merits as compared to selective agents (some shared, some distinctive) and both present certain drawbacks. On balance, although it would be unwise to neglect polypharmaceutical opportunities, assuming that the requisite drug can be made, multi-target strategies appear to be the most promising strategy for future progress.

Table 3 (cont.)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Polypharmacy (drug combinations)</th>
<th>Multi-target agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property, patent issues, financial considerations</td>
<td>Association (and use) patents tend to be weak, especially if one or other of the drugs is generic and/or the property of another firm. Use of additional drugs will increase health-care costs.</td>
<td>Robust protection. Multiple components of pharmacological activity offer additional opportunities for patent strategies compared to selective agents. Costs of mechanistically novel drugs superior to existing agents may be high at launch.</td>
</tr>
</tbody>
</table>

CNS, Central nervous system; SSRIs, selective serotonin reuptake inhibitors.

The pros and cons of polypharmacy and multi-target drugs are indicated for a broad range of characteristics from discovery and experimental characterization to clinical development and therapeutic exploitation. Comparisons are made among these two families of agents as well as to monotherapy with highly selective agents. Multi-target drugs share most of the benefits of polypharmacy yet lack many of their disadvantages and they also display several distinctive benefits of their own. However, they reveal a few drawbacks, notably in their design and discovery.
Novel targets for multi-target and polypharmaceutical exploitation: new vistas for monoaminergic mechanisms

Underscoring the notion that novel monoaminergic mechanisms may still have something to offer in the multi-target treatment of depression, 5-HT4 agonists and D3 antagonists have attracted interest as rapid onset antidepressants (Lucas, 2009) and, as mentioned above, efforts are being made to develop 5-HT7 antagonists (Mnie-Fallili et al., 2011). Although for reasons accentuated herein, it is dubious whether such mechanisms will suffice alone for adequate efficacy, both 5-HT4 agonists and 5-HT7 receptor blockade may potentiate at least some actions of SSRIs (Lucas, 2009; Shelton et al., 2009) and several multi-target monoaminergic antidepressants are currently under investigation. Notably, clinical data support the effectiveness of Lu-AA21004, which inhibits 5-HT reuptake, acts as a partial agonist at 5-HT1A and 5-HT1B sites and as an antagonist at 5-HT3 and 5-HT7 receptors (Alvarez et al., 2012; Katona et al., 2012; Mork et al., 2012). However, it is not yet clear which (if any) advantages it offers over currently available antidepressants.

Another innovative idea would be to couple DA D3 antagonist properties to SSRIs and other antidepressant mechanisms in view of compelling evidence for improvements in a broad spectrum of depression-compromised cognitive domains, such as social cognition, working memory, attention and executive function. Moreover D3 receptor blockade elevates neurogenesis in the hippocampus (which is defective in depression), counters stress-induced drug-seeking behaviour (for example, of cocaine) and promotes motor function in models of Parkinson’s disease (Millan et al., 2007; Millan and Brocco, 2008; Heidbreder and Newman, 2010; Loiseau et al., 2009; Egeland et al., 2012; Watson et al., 2012). Selective D3 antagonists have not yet reached patients, yet multi-target antidepressants possessing D3 receptor antagonist properties could be of particular use for treatment, not only of major depression but also of depressed mood co-morbid with substance abuse, schizophrenia and Parkinson’s disease (see above citations).

Novel targets for multi-target and polypharmaceutical exploitation: non-monoaminergic concepts

Agomelatine still holds its position as a uniquely innovative and clinically proven, multi-target antidepressant reflecting its complementary (perhaps synergistic) agonist and antagonist properties at melatonin and 5-HT2C receptors, respectively. It also possesses anxiolytic properties and appears to promote sleep (De Bodinat et al., 2010; Kasper et al., 2010; Racagni et al., 2011; Catena-Dell’Ossio et al., 2012). Clearly, there remains an urgent need to pursue other multi-target strategies oriented around a non-monoaminergic target for further gains in effectiveness and control of other symptom clusters. In this regard, it is worth mentioning some novel avenues of research (highlighted in Fig. 5), which could profitably be developed along lines evoked above.

First, in light of the above-mentioned use of triiodothyronine for augmentation of tricyclics and, less consistently, SSRIs (Cooper-Kazaz and Lerer, 2008; Connolly and Thase, 2012), it is intriguing that the endogenous (decarboxylated) derivative, 3-iodothyronine behaves like tyramine, phenylethylamine and other trace amines as an agonist at trace amine associated receptor 1 receptors (Sotnikova et al., 2009; Di Cara et al., 2012). Their activation modulates monoamine transport and exerts a variety of other cellular effects associated with potential antidepressant properties and ligands at these sites may also be useful for controlling psychosis associated with depression (Xie and Miller, 2009; Revel et al., 2012a, b). Trace amine associated receptor 1 receptors are a novel and promising site for new classes of multi-modal antidepressant.

Second, as depicted in Fig. 2, there is increasing interest in epigenetic mechanisms in the pathogenesis of depressed states and the broad range of epigenetic processes controlling gene expression independent of DNA sequence (from DNA methylation and histone marking to non-coding RNA control of mRNA splicing and translation) provides a broad palette of potential targets for new classes of multi-modal antidepressant (Millan, 2011; Uher, 2011; Mouillet-Richard et al., 2012; Sun et al., 2012). Of particular interest are histone deacetylase 2 inhibitors, which possess antidepressant properties in rodents, as well as complementary pro-cognitive actions (Graff and Mansuy, 2009; Covington et al., 2010; Day and Sweett, 2012; Lin et al., 2012; Yamawaki et al., 2012). Interestingly, there is evidence that folate (folic acid) is lacking in depression and its deficiency may not only compromise active RNA formation but also methylation of both histones and DNA (Gilbody et al., 2007). Antidepressant-like actions of folate have been reported in rodents and studies are being pursued of its administration alone and together with SSRIs to patients (Taylor et al., 2004; Stahl, 2007; Molina-Hernandez et al., 2011, 2012). On this basis, and in view of the significance of DNA and histone methylation to the mood and cognitive deficits of neurodevelopmental disorders, histone methyltransferases and demethylases, as well
as enzymes controlling DNA methylation, justify evaluation as potential targets for antidepressants (Kramer and van Bokhoven, 2009; Gomes and Joca, 2011; Sanchez-Mut et al., 2012; Millan, 2013).

Third, in addition to ionotropic AMPA and NMDA receptors (vide supra), recent evidence supports a role for various classes of mGluR receptor in the control of mood and, specifically, in depressive states. Thus, blockade of mGluR2 (Bespalov et al., 2008; Campo et al., 2011; Dwyer et al., 2012) and mGluR5 (Hughes et al., 2012; Inta et al., 2012) receptor subtypes on the one hand and activation of the mGluR7 subtype on the other (Palucha et al., 2007; Bradley et al., 2012) is associated with antidepressant (and anxiolytic) properties. Apart from multi-target agents, adjunctive use of mGluR ligands is an attractive possibility (Matrisciano et al., 2008).

Fourth, neuropeptide Y has long been implicated in the response to stress and in the control of mood. Activation of post-synaptic Y1 sites, or blockade of their Y2 presynaptic counterparts, has been associated with antidepressant and anxiolytic properties in rodents (Ishida et al., 2007; Tasan et al., 2010; Gelfo et al., 2012). Interestingly, subthreshold doses of neuropeptide Y and fluoxetine synergistically elicited antidepressant effects (Molina-Hernandez and Tellez-Alcantara, 2011). Finally, suggesting a further dimension to the role of neuropeptide Y, a non-peptidergic antagonist at Y5 receptors was recently found to elicit antidepressant effects (Packiarajan et al., 2011).

Fifth, another intriguing peptide for which data are less extensive is the appetite-stimulating hormone ghrelin, which is secreted by the gut yet enters the brain where it facilitates cognition and counters the

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**Fig. 5.** Novel mechanisms under exploration for multi-target and/or polypharmaceutical exploitation in the improved treatment of depression. Including receptors, transporters and enzymes for degradation, there are about 30 ways of manipulating monoaminergic transmission, of which several – but not all – are already clinically exploited. In addition, there are innumerable, potential non-monoaminergic mechanisms for improving various dimensions of depressed states, although none has yet become available to patients as selective drugs. It should be possible to harness clinically validated mechanisms of antidepressant action [such as 5-HT and/or noradrenaline (NA) reuptake suppression or 5-HT2C receptor blockade] and add on complementary mechanisms (either mono- or non-monoaminergic) to strengthen efficacy, improve tolerance, reduce delay to action and control a broader range of symptoms. An example of a multi-target agent would be agomelatine [melatonin agonist (Ago) plus 5-HT2C antagonist (Ant)] and an example of polypharmacy would be fluoxetine plus olanzapine for treatment-resistant depression. Many more permutations remain to be experimentally and clinically explored (see text). Dependent upon drug availability and other factors, both polypharmacy (drug combinations) and multi-target agents are appropriate vehicles for uniting the mechanisms of action indicated. DA, Dopamine; TAAR, trace amine associated receptor; PAM, positive allosteric modulator; mGluR, metabotropic glutamatergic.
deleterious impact of stress on mood (Lutter et al., 2008; Atcha et al., 2009; Chuang and Zigman, 2010). Although its precise role in the control of anxious and depressed states remains somewhat unclear, ghrelin may possess antidepressant properties and further studies of therapeutic relevance to the control of depression is warranted (Chuang and Zigman, 2010; Carlini et al., 2012; Ishitobi et al., 2012).

Sixth, as mentioned above, there is considerable interest in the influence of nicotinic receptors upon depressed mood, with most attention to date directed towards antagonists at α7β2 receptors – despite the recent disappointment of (S)-mecamylamine as adjunctive therapy for SSRIs (Ledford, 2011; Philip et al., 2012). α7 receptors are likewise of interest in view of their positive influence upon cognition (Graef et al., 2011; Levin, 2012; Millan et al., 2012). Although affinities of α7 ligands at 5-HT transporters, and reciprocally of SSRIs at nicotinic receptors, complicates studies of interactions, there is evidence that α7 receptor blockade potentiates the actions of SSRIs in rodent models of antidepressant properties (Millan, 2006; Andreasen et al., 2012). Although rapid antidepressant actions of the muscarinic antagonist, scopolamine, have been reported, it would appear more appropriate to identify and exploit the underlying cellular substrates – perhaps analogous to those harnessed by ketamine or sleep deprivation (Bunney and Bunney, 2012) – rather than pursue multi-target drugs blocking muscarinic receptors in view of gender differences and their notorious side-effect profile, although allosteric sites may represent a hitherto unexplored opportunity for therapeutics (Drevets and Furey, 2010).

Finally, although not illustrated in Fig. 5, a few words should be devoted to glial mechanisms, long implicated in the pathogenesis of depression (and other CNS disorders) but still not harnessed therapeutically (Czeh and Di Benedetto, 2012). An interesting link has been made to a further potential substrate for multi-modal treatment of depression: p38-mitogen activated kinase, which phosphorylates and increases the membrane expression of 5-HT leading to reduced levels of extracellular 5-HT (Bruchas et al., 2011; Connolly and Thase, 2012). Glycogen synthase kinase-β inhibition remains under consideration as well as a potential antidepressant strategy (Millan, 2009; Connolly and Thase, 2012; Duman and Voleti, 2012). Nonetheless, even for multi-target drugs, the above mechanisms all raise important questions of specificity and safety if they are to be therapeutically exploited for treatment of depression or other CNS disorders.

While mechanistic details of how the above drug classes affect mood and other functions disrupted in depression are beyond the scope of this review (see above citations), they suggest scope for the exploration of novel multi-modal strategies for the improved treatment of depressed states.

Integration of multi-modal pharmacotherapy with ‘alternative’ treatments

Not surprisingly, in view of persistent difficulties in identifying improved pharmacotherapy for depression, there is ever-increasing interest in ‘alternative’ (and, from a network perspective, ‘multi-target’) strategies as diverse as, for example, mindfulness (Marchand, 2012), cognitive behavioural therapy (DeRubeis et al., 2008), light exposure (Crowley and Youngstedt, 2012) and transcranial direct stimulation (Del’Osso et al., 2012). Ultimately, the goal would arguably be to abolish artificial barriers and the knowledge gap between medication and validated, non-pharmacotherapeutic strategies and to unite them in a coherent and evidence-based manner to the profit of individual (subsets of) patients. Thus, a final issue concerns the potential use of multi-target antidepressants and polypharmacy in association with alternative treatment strategies, where medication is not sufficient alone for satisfactory remission. Cognitive behavioural therapy acts at the ‘cerebral circuit’ level rather than homing in on any discrete molecular substrate and it recruits contrasting cerebral mechanisms vs. pharmacotherapy (Kennedy et al., 2007). This supports the logic of its combination with pharmacotherapy for improving efficacy, reducing relapse and enhancing quality of life (Guidi et al., 2011; Ishak et al., 2011; Köhler et al., 2011). While such dual treatment strategies would be difficult to integrate into early development programmes, small-scale pilot trials and post-authorization studies should prove useful in more fully exploring the clinical utility of novel classes of multi-target drug and polypharmacy. Finally, stimulation procedures for alleviating depression might be combined with antidepressant agents in an attempt to improve efficacy (Eitan and Lerer, 2006).

Concluding comments

As compared to highly selective agents, multi-modal therapeutic strategies appear to offer greater promise for the broad-based and improved treatment of depressed states. The systematic pursuit of selective and multi-target agents together with the exploration of novel drug combinations is a reasonable blueprint for satisfactory remission. Cognitive behavioural therapy acts at the ‘cerebral circuit’ level rather than homing in on any discrete molecular substrate and it recruits contrasting cerebral mechanisms vs. pharmacotherapy (Kennedy et al., 2007). This supports the logic of its combination with pharmacotherapy for improving efficacy, reducing relapse and enhancing quality of life (Guidi et al., 2011; Ishak et al., 2011; Köhler et al., 2011). While such dual treatment strategies would be difficult to integrate into early development programmes, small-scale pilot trials and post-authorization studies should prove useful in more fully exploring the clinical utility of novel classes of multi-target drug and polypharmacy. Finally, stimulation procedures for alleviating depression might be combined with antidepressant agents in an attempt to improve efficacy (Eitan and Lerer, 2006).
for future progress. There is nothing inherently radical in all this inasmuch as multi-modal strategies are already a focal point for the improved control of complex disorders as diverse as cancer, malaria, Parkinson’s and Alzheimer’s disease (Toda et al., 2003; Millan, 2006; Van der Schyf et al., 2007; Petrelli and Giordano, 2008; Piazzì et al., 2008). On the contrary, it is surprising that multi-modal thinking is not more predominant in the field of depression ‘R’ and ‘D’ as a potential foundation for future progress. While combinations of clinically characterized compounds remain feasible and potentially important (as illustrated by second-generation antipsychotics plus SSRIs), the development of mixtures of two new drugs is more challenging and there are several limitations to polypharmaceutical approaches for treating depression. Conversely, while not ignoring the chemical difficulty of multi-target drug design and their invariant ratio of component pharmacological activities, they share many of the benefits of polypharmacy while lacking a number of important drawbacks. All things considered, multi-target agents may be the most attractive route towards novel and improved antidepressant agents. Currently, they are exemplified by the mechanistically innovative agent, agomelatine, but it is to be hoped that complementary multi-target agents with other advantages for treating additional dimensions of depression will eventually become available. Together with improvements in translational measures of drug actions between rodents and humans, more objective biomarkers of incipient and actual depressed states and innovations in clinical evaluation of new drugs, a shift in mindset from highly selective to multi-modal treatment strategies may help revitalize a domain greatly in need of further progress in view of the insufficient current treatment of major depression.

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Complementary strategies for improving the treatment of depression

1029


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