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Triple reuptake inhibitors (TRIs): do they promise us a rose garden?

Major depressive disorder (MDD) is a highly prevalent psychiatric disorder and is reported as one of the most leading cause of disabilities and markedly contributes to a significant global burden of the disease worldwide. It has been reported that MDD has lifetime prevalence of almost 16% in the USA [1]. MDD significantly alters the quality of life of the patients, productivity at the workplace, and has adverse effects on interpersonal and familial relationships. In a world with increasingly demanding service-oriented economies, individuals would be more vulnerable to the adverse effects of depression on cognitive, emotional, and interpersonal levels. Depression also leads to considerable maladaptive illness behaviours with an increased risk of cardiovascular diseases, neurocognitive disorders, and increased health care utilization with comorbid chronic illnesses.

Most current antidepressants *selectively* target monoamines serotonin, norepinephrine, or dopamine, which was linked to deficiencies in neurotransmission in the brains of depressed individuals while having limited effects on muscarinic and histamine receptors [2]. Other antidepressants which enhance norepinephrine and serotonin neurotransmission via other mechanisms have also been developed. These medications include mirtazepine (presynaptic alpha-2 adrenergic antagonist), as well as trazodone and nefazodone (primarily presynaptic and postsynaptic 5-HT₂ antagonists). Over the years, although the data indicated the important role of mesolimbic dopamine in moderating motivation and reward-related behaviour which are typically disrupted in depression; dopamine transmission was given less attention in the management of depression [3]. Similarly, antidepressants which have been shown to sensitize mesolimbic dopamine receptors, have led to the hypothesis that enhancing synaptic dopamine availability might lead to faster antidepressant responsiveness [2]. One of the major problems with current antidepressants is that almost 50% of depressed patients fail to achieve remission with their first-line antidepressant use. Another major issue with the current antidepressants is the fact that their slower onset of action with several weeks or months of treatment before any clinical improvements has been observed and reported. Therefore, a clear unmet pharmacological need for better, faster, and stronger antidepressants that have a mechanism of

action beyond of serotonergic and noradrenergic neurotransmission enhancement is evident.

Rather than individual proteins, receptors, or neurons; among the emergent properties of disrupted brain networks are mood, cognition, and other functions of individuals with depression. Although these neural networks are presumed to be resistant to lasting effects on mood from environmental challenges, vulnerability to mood perturbations due to stress is influenced by interacting genetic, epigenetic, and developmental factors [4]. Depending on an individual's vulnerability; environmental challenges (particularly intense stress) can impact intracellular signalling, mechanisms of gene expression, neurotrophic mechanisms, neurogenesis, synaptic function and plasticity, and remodelling of neuronal cells to disrupt brain networks with serious consequences as in the case of depression [5]. Over time, networks controlling mood may phase-shift into a new configuration that is difficult to reverse. If possible, prevention or treatment of MDD at earlier stages would be ideal. Drugs specifically acting on crucial systems such as the serotonin system can be useful in limiting the duration of aforementioned neural network disruptions. On the other hand, drugs acting on several monoamine systems might more effectively restore dysfunctional networks in severe and chronic disorders through *mirroring* the multi-system operation of the brain [6–8]. Along with greater severity and chronicity, increasingly difficult-to-treat disorder may then be refractory to monoaminergic approaches and would require the targeting of more fundamental mechanisms to restore disrupted brain networks back to normal functioning.

Following the serotonin and norepinephrine reuptake inhibitors' (SNRIs) relative success in treatment of MDD, researchers have pursued the idea of developing novel drugs blocking all three monoamine transporters, namely serotonin, NE, DA reuptake inhibitors, or triple reuptake inhibitors (TRIs). This concept was based on the positive role of DA on the reward system and the fact that anhedonia was a prominent symptom in a subset of MDD patients, especially those with melancholic depression. This hypothesis was further tested and supported by positive clinical augmentation studies with DA-enhancing drugs [9]. During the past decade, several TRI candidates have been developed and examined in clinical

practice. Amitifadine (DOV-21,947 or EB-1010), which was among the first TRI drug candidates, preferentially enhanced 5-HT with 1:2:8 potency rankings for the inhibition of SERT, NET, and DAT, respectively [10]. Although preliminary clinical studies suggested amitifadine had antidepressant effects [11]. Whether the addition of dopamine transporter blockade results in enhanced efficacy compared with currently available antidepressant drugs remained to be further examined. Other efforts to develop more balanced TRIs with similar K_i values for SERT, NET, and DAT have also failed. Two compounds, NS-2359 (GSK-372475) and liafensine (BMS-820836), were evaluated in phase 2 clinical studies, but both programmes were terminated. In a large phase 2 programme with 900 patients, NS-2359 was not found efficacious and well tolerated, while comparators paroxetine and venlafaxine significantly separated from placebo [12]. Results are mixed regarding whether broader spectrum agents or highly serotonin selective agents confer the best efficacy. Controversy continues as to whether a combination of both SERT and NET inhibition represents a more effective antidepressant treatment than drugs that target SERT or NET alone, particularly for SSRI resistant depression, severe depression, melancholic depression, and hospitalized patients with endogenous depression. In fact, it is plausible that TRIs that minimize blockade at histaminergic, cholinergic, and alpha-adrenergic receptors may yield the most *favourable tolerability* of all antidepressants with less sexual side effects than SSRIs or SNRIs. By way of example, bupropion has long been used to treat antidepressant-related sexual dysfunction, presumably through its dopaminergic effects [13]. The addition of dopamine reuptake inhibition to an optimized TRI medications may reduce specific symptoms, improve response and remission rates, and might expedite the onset of antidepressant effect [2, 8]. These putative benefits may be particularly evident in a fraction of depressed patients which are unresponsive to previous full-dose and duration antidepressant treatment, and in phenotypes of depression with broader disruption of monoamine neurotransmitter systems, and also in comorbid conditions which implicate reward-network dysfunctions [14, 15]. In other words, TRIs might have better efficacy in a well-defined subset of depression patients with prominent symptoms of anhedonia. In patients receiving SSRI or SNRI, switching to a TRI may *counteract* hypodopaminergic effects which may result when serotonergic system is selectively enhanced [15]. However, the existence of dense connections between monoaminergic neurons in the human brain makes the clinical profile of a combination of mechanisms difficult to predict. It is still not known how the further addition of DAT inhibition would affect the cardiovascular condition of depressed patients. The main concerns with these drugs have been how to avoid exaggerated

dopaminergic stimulation and abuse liability. It was known that addition of substantial NET inhibition to SERT inhibition produces dose-related increases in blood pressure, heart rate, and impaired orthostatic reflexes [16]. In addition, further DAT inhibition would raise the potential for prescription drug abuse liability. The interactions between monoamine systems implicates that higher levels of DAT inhibition are required to activate reward pathways in the presence of high SERT inhibition [16]. A slow rise to maximum concentrations and slow clearance from the brain should minimize the potential for abuse that may accompany DAT inhibition of over 50% at tolerated doses, improve tolerability, provide more effective management if treatment adherence is less than optimal, and greatly diminish the potential for withdrawal reactions with abrupt cessation of treatment.

Like other classes of antidepressant medications, TRIs hold promise for a variety of other therapeutic indications. One emerging area of research indicates the potential antinociceptive effects of triple inhibitors, which is expected given the numerous data supporting the utility of TCAs and SNRIs for pain syndromes. Pre-clinical research with bicifadine demonstrated its antinociceptive effects in animal models of acute, persistent, and chronic pain syndromes. These effects were reduced in some experimental conditions by the co-administration of sulphide (a dopamine-2 receptor antagonist), suggesting that *enhancement of dopamine neurotransmission* is important for the full antinociceptive effect of bicifadine [17]. In a phase IIa pilot study in Alzheimer's disease, tesofensine treatment was associated with cognitive improvements [18, 19]; although it has been proposed that tesofensine indirectly stimulates cholinergic neurotransmission, the physiological mechanism of this observation remains to be unclear. Weight loss has been observed as an adverse event in studies of tesofensine [20], prompting further research for the indication of obesity. One published preclinical study describes the effect of the balanced triple reuptake inhibitor DOV 102,677 in reducing volitional alcohol consumption in ethanol-preferring rats without decreasing food or water consumption [21]. However, it should be noted that monoamine reuptake inhibitors have historically performed better in animal models of addiction than in human clinical trials. However, it is possible that agents which inhibit dopamine reuptake might offer improved efficacy in substance use disorders due to the link between dopamine and reward-circuitry related behaviours.

There is currently a crisis in antidepressant drug development, along with drug development for all neuropsychiatric disorders [22]. Many biopharmaceutical companies have reduced or paused investments in antidepressant drug development due to the fact that antidepressant drugs tend to fail in late-stage clinical trials after a significant investment has been made. The

explanation for this investment retreat is multi-dimensional: paucity of novel validated targets, a nosology that is not based on pathophysiology that impedes progress in translational research, the lack of predictive animal models, the absence of biomarkers, the challenge of differentiating active drugs from placebo and the even greater challenge of differentiating between existing drugs, and finally the regulatory challenges. Drug development in MDD alternatively could be of broadly targeted therapies such as TRIs that aspire to the efficacy of existing agents with the additional targeting of dimensions of psychopathology not adequately treated by existing antidepressants. If specific efficacy contribution is clearly characterized for a new treatment, it should be capable of recognition in the drug labelling. Regulatory agencies should more strongly advocate that clinical development would no longer follow the traditional path of placebo-controlled studies for an indistinguishable efficacy claim in depression treatments. Regulatory agencies should also encourage efforts to identify effects on the domains and dimensions of psychopathology through which superior efficacy was achieved.

Conclusions

Given the devastating and costly impact to society, families, and individuals of inadequately treated MDD, it is imperative that there is continued investment in the discovery and development of new antidepressants. The addition of an appropriate dopaminergic component to the 5-HT and NE components of existing widely used monoamine-based antidepressants could offer superior improvement of reward-network dysfunction and restoration of positive mood. In addition to numerous and divergent biological factors, considerable heterogeneity in symptoms, comorbidity, and etiology in depressed patient cohorts are present. Advances in the circuit level understanding of stress vulnerability *versus* resilience, of endophenotypes of MDD characterized by dimensions of psychopathology associated with neurocircuitry dysfunctions, and of antidepressant response [23] should enable the identification and validation of translational biomarkers of specific neurocircuitry dysfunctions for use in novel antidepressant development. The functional impact of different reuptake inhibitors on the activation state of relevant brain neurocircuits could be relevant on the individual patient level and may identify neuroimaging endophenotypes or biosignatures associated with differential response to a TRI relative to standard-of-care antidepressants. Combination of pharmacological and non-pharmacological treatments [deep brain stimulation, transcranial magnetic stimulation, and cognitive behavioral therapy], is a promising therapeutic approach that could benefit from larger systematic prospective studies. However, in the near future, it seems evident that these discoveries would still continue to rely on empirical data and serendipity rather

than being based on a thorough understanding of the disorder etiologies and associated neural circuitries. Nonetheless, basic research in understanding mechanisms of depression and other psychiatric disorders should always remain a high priority in the scientific community.

Disclosure statement

No potential conflict of interest was reported by the authors.

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