Article

Rapid onset of action of mirtazapine: a review illustrating its benefits and risks over SSRI

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ABSTRACT

Depressive disorders have become a serious illness affecting millions worldwide, which prominently affects day to day life activities of patients affected with the disorder. It becomes a long term illness gradually requiring prompt therapy to prevent certain risk associated with the illness chiefly suicidal risk. Traditional antidepressants generally required weeks to months to generate any response from patients, having delayed onset of action which may become cumbersome and quite expensive for the population in need. However, the introduction of certain antidepressants with a faster onset of action, such as mirtazapine changed the conventional approaches. Electronic search was performed to identify and include relevant studies done under topic of interest since from 1999 to 2020. This paperbriefly reviews the various published literature on mirtazapine to come up with sufficient evidence illustrating its faster onset of action compared to several other antidepressants using certain comparison studies emphasizing its benefits along with risk.

Key Words: Antidepressant, mirtazapine, rapid onset, SSRI, suicidal risk

Received: 25/7/2020; Revised: 29/7/2020; Accepted: 10/9/2020

Introduction

The emerging and rise in antidepressant use brought us the selective serotonin reuptake inhibitors(SSRIs)in market in the 90s, which proved to be much tolerable and safer than the older drugs such as MAOIs and TCA and, therefore, partially replaced the older antidepressants in the pharmacological therapy of depression [1]. The introduction of newer generation antidepressants, preferably with dual target actions, such as mirtazapine and venlafaxine which affect both the serotonin and norepinephrine systems in the central nervous system (CNS), but devoid of the anticholinergic

and cardiovascular side effects made them the drugs of choice replacing the TCAs. However, multiple advances in studies are still required to achieve an ideal drug which constrains a rapid onset of action, achieve remission along with abstaining relapse with minimum side-effects [2] . The therapeutic benefits of antidepressant response in any patient may appear different and take as long as months to show any benefits of therapy. However, in lieu of this prevalence, various meta-analysis and reviews have shown a much more rapid onset of action for certain antidepressants as soon as within the first week of therapy initiation [3,4].

Antidepressant onset of action becomes important because suicidality presents itself as a major risk factor during the course of the illness of depression. It has been suggested that suicidal tendencies may be more prevalent in the earlier weeks of antidepressant treatment as compared to succeeding months[5]. However, it may remain constant with subsequent time due to sustained outcomes with treatment, especially with newer antidepressants. This necessitates the importance of rapid response to antidepressant treatment and to maintain it steady to benefit the patient [6].

Pharmacological profile of mirtazapine

Mirtazapine belongs to a class of noradrenergic and specific serotonergic antagonist (NaSSA). It acts as an antagonist at certain specific serotonergic receptors, including 5-HT2 and 5-HT3 increasing serotonin release[7]. It also works as an antagonist at central a2 adrenergic receptors increasing norepinephrine release [8].

Another main view of the pharmacological effect of mirtazapine is characterized by its varying effects on serotonin receptors. This occurs as a result of 5-HT1A agonistic effects which account for increase serotonergic transmission. It also acts as a potent antagonist at 5-HT2 and 5-HT3 receptors that differentiated this drug from various other antidepressants in terms of anxiolytic and sleep improving effects. Additionally, antagonism of these receptors also helps to avoid certain SSRI related adverse effects such as insomnia, sexual dysfunction, nausea, etc[9].

Mirtazapine has very little affinity for muscarinic and cholinergic receptors. It also has very little affinity for dopamine receptors with no effect on dopamine reuptake. However, it acts as a potent antihistaminic agent responsible for its beneficial effect on sleep centers giving additional sedative and hypnotic effects in clinical doses [10].

Methodology & Search strategy

A systematic literature search was performed using databases of PUBMED/MEDLINE, Google scholar, and the Cochrane library restricted to the English language. Searches were performed using various terms as singular or in combination pertaining to the topic of interest such as ‘antidepressant’, ‘mirtazapine’, ‘depression’, ‘onset of action’ and ‘mechanism of action’. The relevant studies were identified published within 1999-2020 and reviewed thoroughly. Additionally, the references of selected literature reviews was also manually screened for possible inclusion in the study.

Time to onset v/s time to response

Rapid onset is not the same as rapid response. The response is produced when a patient on target drug shows positive outcomes irrespective of drug's efficacy and timing of action. On the other hand, the onset of action is held accountable on the drug's properties only. Every patient is expected to show certain response to the drug relevant to its onset of action.

Responses are highlighted when there is at least a 50% reduction in the disease state. Responses can be early and short-term as well as long-term which are highly acknowledged. Illnesses like depression requires long-term and sustained positive responses to improve the well-being of patients suffering. Hence, responses should be measured whether they are an outcome of a drug's mechanistic action or ordinarily a placebo effect [11].

The onset of action is said to have occurred when there is at least a minimal response for the first time by the patient under the target drug. Concerning depression, these responses can be measured in terms of widely used depression rating scales such as HAM-D or MADRS. In long-run, remission is highly appreciated in order to control the disease. A score of <7 is considered a positive remitter as per HAM-D statistics [12].

Faster onset of action: results from eligible studies

Rapid onset of efficacy, additionally, has been proven to be a major predictor of remission in patients as suggested by a randomized controlled trial. It states that early onset of efficacy of drugs such as mirtazapine and paroxetine proved to be providing a stable response later in the course of illness as well as manage to produce remission [13]. This is compatible with the results drawn by another study involving mirtazapine as the sole drug to establish remission in patients treated with the drug with respect to its onset of action. Improvements were found with respect to late insomnia, somatic symptoms and general behavior. This was proved by HDRS scores at the end of 6 weeks confirming remission status [14].

Comparison to SSRI

Second-generation antidepressants, i.e, SSRI, provide their antidepressant effect by acting on serotonin transport(SERT) via inhibiting serotonin reuptake.[15] This occurs initially with serotonin levels increasing in the somatodendritic area of the neurons. With repeated dosing for longer periods, i.e, around 3 weeks, the sustained concentration of the drug further increases serotonin causing desensitization of 5-HT1A auto receptors. This desensitization of the auto receptor regulating serotonin release explains the late onset of action of SSRI [16].

However, newer/third-generation antidepressants such as mirtazapine causes a rapid release of 5-HT neurotransmission via a combined effect on noradrenergic as well as 5-HT neurons which are proposed to be involved in the pathophysiology of depression [17].

Mirtazapine binds to a2 auto receptors on the inhibiting the noradrenergic neurons overcoming negative feedback system and thus increases the NA release which further leads to 5-HT release as a result of NA neurons projecting towards the 5-HT

neurons at raphe nuclei. This eventually enhances NA as well as 5-HT concentration in the forebrain [18].

Randomized trials have led to the fact that mirtazapine is indeed a fast-acting antidepressant compared to widely used SSRI class of drugs due to its unique mechanism of action. Mirtazapine involves synergistic action on increasing noradrenaline as well as 5-HT release from the presynapatic terminals which essentially works in favor of increased neurotransmission [19].

This was acknowledged by yet another study performed in comparison to a widely used SSRI citalopram which generated convincing results statistically. Both drugs under study were highly tolerated and efficacious, nonetheless, mirtazapine was found to have a much faster onset of action as displayed by lower HDRS scores at the end of 2 weeks of initiating therapy compared to citalopram [20].

The same results were drawn by another double-blind controlled study that used SSRI such as citalopram, fluoxetine as well as paroxetine in contrast to mirtazapine. Early-onset in addition to early response produced by the mirtazapine group led to the interpretation that mirtazapine is indeed a faster-acting drug in contrast to SSRI. Additionally, the % of remitters demonstrated by HDRS scores also were larger in the mirtazapine group of subjects [21].

Risks involved with drug

Adverse effect profile:[22,23]

Most common: dry mouth, increased appetite, increase weight, fatigue and headache, malaise, and somnolence.

Less common: flatulence, sweating, sexual dysfunction, nausea & vomiting, insomnia, diarrhea, and tremors

Rare: hypertension, ECG abnormalities, dermatitis, agranulocytosis

USFDA BLACK BOX WARNING: increased suicidal risk especially below 25 years of age.

Overdose:[24,25]

Overdose complications seem to be less severe as compared to older antidepressants such as TCA and MAO inhibitors.

Ingestion of mirtazapine in doses as high as 350 mg and greater reports major complication as drowsiness and reduced consciousness levels possibly due to antihistaminic effects. Another main feature occurring is tachycardia which does not necessarily possess a dose response relationship.

Cardio toxicity does not seem to be a primary feature of mirtazapine toxicity as seen in TCA and SNRI. The same applies to seizure manifestations which can be seen with SSRI additionally but not with mirtazapine.

Interactions:[26,27]

Major enzymes involved in the metabolism of mirtazapine and its metabolites are CYP1A2, CYP3A4 and, CYP2D6. However, it does not act as an inducer or inhibitor of any CYP isoform unlike other antidepressants, and thus have a low risk for major drug interactions.

Certain drugs affecting CYP2D6 isoforms including paroxetine and fluvoxamine altering mirtazapine drug concentration are thus advised to be given with caution along with mirtazapine.

-Phenytoin and carbamazepine also affect mirtazapine drug levels via CYP3A4 induction and hence decrease the AUC of the target drug.

-Smoking also seem to affect mirtazapine drug concentration in that smokers presents with reduced plasma concentration of drug compared to non-smokers as a result of CYP1A2 induction.

-it is also advised to use caution while prescribing mirtazapine with other sedative and hypnotics due to the additive effect of drugs.

-it is also advised to keep a lag period of at least 2 weeks while shifting from MAO inhibitors to mirtazapine and vice-versa.

Discussion

Conventional approaches of drug therapy to depression highly emphasized to slowly titrate the drug until complete or at least partial response occurs, keeping in mind the emergence of adverse effects which may take months. However, certain placebo controlled trials generated enough evidence regarding the first few weeks of treatment to be considered while observing responders. Almost 60% of individuals showed improvement within the first two weeks. Placebo controlled design also worked in favor of diminishing the probability of the responses to be a placebo effect [28].

Sustained responses are required to completely overcome the disease which can be predicted by the early response to treatment. Conversely, it is also suggested that initial non-responders are difficult to achieve remission later as well [29]. Mirtazapine, having a faster onset of action worksperfectly on the radar to initiate early responses which benefits the patients in long-term which has been shown to be superior to its counterparts fluoxetine and paroxetine [30].

Hence, early improvement seen in patients become extremely necessary to predict whether a response will occur or not followed by remission. This is in concordance with the results of a post-hoc analysis implemented to ascertain the fact that early responses are undeniably followed by early improvement which takes place with the utilization of faster acting drugs [31].

Conclusion

Overall implication arose from the research works in consideration of requiring a rapid response to the antidepressants to prevent risks associated with the disease along with achieving remission. Mirtazapine can be solely chosen for this purpose due to its ability to have a faster onset of action compared to conventionally used substitutes.

Conflict of Interest

Authors declare that there is no conflict of interest.

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