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Long Term & Short Term Dose Dependent Effect of Mirtazapine- A Case Report

Madhav G Raje[1*] and Anurag Raje[2]

[1]Consultant Psychiatrist & Psychotherapist, Mahakali Hospital, India

[2]Intern, NKP SIMS, Nagpur, India

[*]**Corresponding author:** Raje MG, Consultant Psychiatrist & Psychotherapist, Mahakali Hospital, Nagpur, India, Tel: 919822947102; E-mail: drmadhavraje@gmail.com

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Abstract

Mirtazapine is considered to be safest and versatile antidepressant. However, sedation is known to be dose dependent side effect. 7.5 mg/day mirtazapine induces more sedation than 15 mg/day mirtazapine. There is no other side effect of mirtazapine which is reported to be dose dependent.

Case Report: Here is a case, where dose dependent effect and side effect is detected. A 38-year-old married female reported with array of recurring symptoms like dysphoria, insomnia, loss of appetite, burning all over, uneasiness, increased frequency of micturation and stool, irritability, frustration, weeping often. She was symptomatic since last five to six years, despite regular psychiatric treatment. Her earlier psychiatrist had expressed inability to treat recurrence and intensity of her symptoms. She was kept on mirtazapine 7.5 mg per day to begin with. She responded favorably. Dose of mirtazapine was increased to 15 mg/day to optimize the standardization of dose. Optimum standard dose should be given to achieve optimum, long lasting effects and recovery. Within one to two days she complained of inability to pass urine. Her complaint was specific that she was not able to empty her bladder completely. After completing the act of micturation she used to experience much discomfort in pelvic region. Further investigations revealed significant urinary retention. Lowering of dose brought her relief immediately. Follow up for three years now reveals that patient is asymptomatic with the dose of 7.5mg Mirtazapine. It is remarkable to find Single antidepressant mirtazapine has given long lasting asymptomatic status, despite previous use of multiple antidepressants.

Conclusion: Mirtazapine with dose of 7.5 mg per day effectively could treat recurring symptoms of a female patient and offered steady asymptomatic clinical picture. Increase in dose up to 15 mg/day caused significant side effect of urinary retention against the conventional belief of rise in dose of mirtazapine would increase the relief.

Keywords: ***Low dose efficacy; Dose dependent side effect; Mirtazapine; Rare adverse effect; Female urinary retention; Broad spectrum antidepressant***

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1. Introduction

Mirtazapine is considered to be a safest and versatile antidepressant [1,2]. Its efficacy is similar with that of SSRI [1]. Search in Indian literature reveals insufficient data on use of Mirtazapine. Globally recommended therapeutic dose of mirtazapine is 15 mg to 45 mg per day [3]. However, it's mostly used as add on antidepressant for short term augmentation in the dose of 7.5 mg per day [2].

Few have mentioned efficacy & wide use of Mirtazapine for more than 1 to 2 years or long term duration [4-6]. However, Montgomery et al. [7] published in 1998, Thase ME et al. [8] published in 2001 had reported continuation phase treatment of Mirtazapine. Both of them reports that Mirtazapine is effective & well tolerated for long term use [7,8]. But these and similar studies have not reported use of mirtazapine for more than 2 years. This case study reports safe use of mirtazapine alone for more than 3 years continuously.

Kasper S [9] has observed in 1995 that mirtazapine is effective to broad range of patients. One may consider Mirtazapine as a 'broad spectrum antidepressant' like that of broad spectrum antibiotic.

Common side effects of mirtazapine are weight gain and sedation. Its antagonistic action on 5HT3 and H1 receptors [10,11] is attributed for these side effects. Other less common side effects of mirtazapine are (head to toe) giddiness, confusion, swelling over face/feet, eye pain, red eye, difficulty in breathing, dry mouth, rash/itching, tightness in chest, gastrointestinal disturbances like nausea/vomiting, constipation, weakness, loss of libido, arthralgia, uneasiness, urinary retention, etc. In most cases side effects disappear after couple of days [11] despite continued medication. Sedation is known to be dose dependent side effect. 7.5 mg/day mirtazapine induces more sedation than 15 mg/day mirtazapine [12].

Here is a case where Mirtazapine is continued for more than 3 years without any side effects, like weight gain, somnolence, metabolic abnormalities. This case is significant in following aspects; 7.5 mg per day is used as starting & maintenance dose for continuation phase treatment, increase in dose to therapeutic level attribute urinary retention, this case also highlights that mirtazapine can be used as a single independent (not add on) antidepressant for continuation phase treatment. It can be used for "difficult patients to treat".

2. Case Report

A 38-year-old mother of two children, weighing 65 kg, a part-time laborer, with caring and supporting [occasional significant family tensions], nuclear family presented with array of 'changing symptoms'. Symptoms were, all day long dysphoria, lack of sleep, loss of appetite, burning all over body, indigestion, body ache, chest pain, uneasiness, increased frequency of micturation and stool, headache, frustration to the extent of weeping at times, irritability. She was experiencing these symptoms with fluctuating intensity, for five to six years. She had over-concern for her health issues fulfilling the criteria of hypochondriasis. Occasionally, she experienced intense uneasiness, fear of dying, palpitation. History suggestive of obsessive compulsive features, hypochondriasis, phobia, and dysthymia was noticed in detailed psychiatric interview. Detailed psychiatric interview diagnosed her as suffering from obsessive compulsive spectrum disorder [OCSD], dysthymia, and benzodiazepine dependence.

Past history revealed that she was taking treatment from psychiatrist for more than two years. She was prescribed clonazepam, etizolam, and olanzapine regularly for more than two years. But her symptoms used to recur quite often. Her symptoms were mostly uneasiness, changing somatic complaints like chest pain, headache, backache, increased frequency of micturation. She also complained of lack of sleep, irritability, nervousness repeatedly. As a result of these varying symptoms she used to get impatient and intolerant. She used to express her frustration, lack of relief to her doctor. Hence she used to visit her doctor every now and then, even much before her next appointment. After more than a year, her treating psychiatrist expressed his frustration of offering her total relief. She remembers him telling her to seek another psychiatrist's help. According to her past history and clinical picture she was categorized a 'difficult patient to treat'.

Blood investigations of the patient revealed hemoglobin 11.6 g/dl, serum prolactin 7.5 ng/ml, urea 22.72 mg/dl, creatinine 0.73 mg/dl, Na 136 mEq/L, K 3.2 mEq/L.

In view of persistent symptoms, especially of insomnia, anxiety, hypochondriac thoughts, she was put on sertraline, clonidine, and diazepam. Psycho education clubbed with supportive psychotherapy was offered simultaneously [APA 2004 guidelines assert]. Her insomnia and dysphoria as a result of lack of sleep was treated in the first consultation by paradoxical intervention [a psychotherapeutic module] effectively.

The patient responded partially, i.e. symptoms like insomnia, uneasiness, reduced. But symptoms like loss of appetite, frequency of micturation, burning over chest, headache, dysphoria, hypochondriac thoughts did not improve for almost two to three weeks. Her increased frequency of micturation and amenorrhea did not improve over a month's period, so was referred to gynecologist. Gynecologist found nothing significant on clinical and sonography examination and prescribed alkalizer to alleviate symptoms. Micturation related symptoms recovered after six weeks, on its own.

She was kept on sertraline 100 mg, diazepam 10 mg, and gabapentin 300 mg, per day for 11 weeks [clonidine which was prescribed for sedation and anxiety was withdrawn after two weeks]. There was partial improvement. But, symptoms like disturbed sleep, delay in passing urine, body ache, giddiness, fear of going out, etc. fluctuated significantly and persisted even after treatment for 11 weeks. So sertraline [SSRI] was gradually tapered off and mirtazapine was introduced. Her anxiety responded favorably and within two to three day in response to the beginning dose of 7.5 mg once a day mirtazapine at night. Diazepam, gabapentin were continued in the same doses as earlier. However her pain did not respond, so dose of mirtazapine was increased to 15 mg/day after six weeks. Within one to two days of starting 15 mg/day mirtazapine, she started complaining of increased frequency of micturation, discomfort and fullness in lower abdomen, associated with passing small amount of urine every time, an indication of overflow incontinence [inability to pass urine]. This increased frequency of micturation disturbed her sleep, bowel movements too.

Looking at the patient heightened symptomatic picture, she was referred to gynecologist again. On Ultra sonography; this time, gynecologist noticed significant post void residual urine (more than 100 ml). On the basis of clinical judgment, instead of referring her to urologist, dose of mirtazapine was reduced to 7.5 mg immediately. Next day she reported relief. On subsequent days, she reported improved bowel movements, improved feel of evacuation and symptoms related to passing

urine reduced completely. She was asymptomatic with 7.5 mg of mirtazapine once day at night, with gabapentin 300 mg once a day, diazepam 5 mg OD in the next follow up.

Follow up report: Duration is of more than three years. Frequency of follow up is every month. She was kept on same dose mentioned above for six months. After six months Diazepam was tapered to 2.5 mg per night. So for continuation phase treatment she is kept on Mirtazapine 7.5 mg, Gabapentin 300 mg, Diazepam 2.5 mg per day for more than three years. Dose could not be tapered off further because of her resistance and occasional and less intense symptoms/partial relapses. Clinically she is mostly asymptomatic, except occasional disturbed sleep. Her most frequent earlier complaints like uneasiness, body ache, G I disturbances, worries, dysphoria, loss of appetite, burning all over body, hypochondriac thoughts, negative thoughts, palpitation, fear of dying, etc. are not reported at all despite family tension.

3. Discussion

Core mechanism of action of antidepressants, may be tricyclic antidepressants [TCA] or Specific serotonin receptor inhibitors [SSRI] is potentiating serotonergic transmission. That means, both nor epinephrine [NE] reuptake inhibitors and serotonin reuptake inhibitors work to enhance serotonergic function. However, mirtazapine is a receptor blocking drug rather than uptake inhibitor and enzyme inhibitor unlike other antidepressants. Hence it is called noradrenergic and specific serotonergic antidepressant [NaSSA]. It blocks alpha 2 adrenergic receptors (auto and hetero), 5HT receptors which are presynaptic, thereby facilitates increased release of noradrenalin and serotonin. It also blocks the 5HT-2 and 5HT-3 receptors which are post-synaptic. Thus it spares action on 5HT1, resulting in specific serotonin release activity. It is a partial agonist of 5HT-1, resulting in increase in transmission through 5HT-1. At lower dose, mirtazapine has more affinity with histamine receptors, thus causes sedation. But at higher doses it does not block histamine receptor, so causes less sedation [14]. At higher doses, mirtazapine increases noradrenergic transmission. It may be because half-life of mirtazapine is 37 hours and 26 hours in case of female and male respectively [15].

Overwhelming anxiety, psychic element of anxiety, repeated somatic complaints, disturbed sleep and experience of partial relief even with poly-pharmacy were the reasons behind selection of mirtazapine [16,17].

However, effect of mirtazapine is found different at 7.5 mg than that of at 15 mg. At 7.5 mg mirtazapine shows agonistic effect on histamine receptors (H1) and antagonistic effect on alpha 2 adrenergic receptors. Apha 2 c receptor is situated on adrenal medulla. It causes inhibition of catecholamine. Antagonistic action of mirtazapine on alpha 2 c causes release of noradrenalin. This increased surge of noradrenalin has attributed to urinary retention in this case. At higher doses like 15 mg a day, it sans partial effect on H1 receptors, but has significant effect on serotonergic and noradrenergic receptors. So noradrenalin release increases [17]. It is because of this increased release of noradrenalin, constriction of sphincters, i.e., of bladder and bowel might have taken place in this patient. Thus, constriction of sphincters has caused symptomatic urinary retention. Despite starting dose of mirtazapine is usually 15 mg per day [11], it is found that 7.5 mg per day dose of mirtazapine not only relieved symptoms in this case but maintained recovery as well.

Pharmacokinetics of mirtazapine is age and gender dependent [14]. Female and elderly show higher plasma levels. It is rapidly absorbed when taken orally [11]. Plasma concentration is achieved within one to two hours. 50% of drug's

bioavailability is achieved within two to three hours, since mirtazapine is metabolized through first intestinal and hepatic bypass mechanism. Hence, unlike other antidepressants mirtazapine start therapeutic effect within first week [12]. Male under 48 years, require more dose than female to have equivalent plasma concentration. Meaning young female absorb mirtazapine faster and maximum plasma concentration is reached earlier than male with relatively lower dose.

Mirtazapine is also reckoned to reduce obsessive compulsive symptoms hence replacing SSRI by mirtazapine could not have accelerated OCSD symptoms. Additionally; issues of poly-pharmacy and issue of treating 'difficult patient' could have been dealt with by mirtazapine [16]. So, Mirtazapine was the real answer to many questions, may be like "broad spectrum antidepressant".

Urinary retention is not one of the commonly reported side effects, though occasionally it is observed in psychiatry practice [12]. Data available on epidemiology of female urinary retention is also not adequate [3,4]. Urinary retention in female is more uncommon. Antidepressant like mirtazapine which belong to Nor-epinephrine specific serotonin receptor inhibitor [NaSSA] class may rarely cause urinary retention. However, dose dependent phenomenon of this side effect is not known.

Unlike sedation [11]; dose dependent urinary retention has been reported by me [same case earlier] [18]. Hence, case of urinary retention by higher dose of mirtazapine is worth to be noticed. Another noticeable feature of this case is 7.5 mg per day starting & maintenance dose of Mirtazapine. Meaning starting & maintenance does is same. This case also highlights that low dose of Mirtazapine can be used for continuation phase treatment and be used as independent antidepressant.

4. Conclusion

7.5 mg per day dose of mirtazapine is an adequate dose to start with & to maintain with continuation phase treatment of dysthymia with obsessive compulsive spectrum disorder. Mirtazapine can be safely given for more than three years. 7.5 mg per day dose of mirtazapine alone effectively avoided polypharmacy and maintained good clinical long lasting outcome.

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