

Induction of Psychosis by Cyclobenzaprine

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ABSTRACT ~ Due to the stringent regulatory environment for therapeutics, common side-effects of drugs in the general population are largely well-documented. This is however less the case with certain patient subgroups who may exhibit significant adverse responses to therapeutics that are otherwise well-tolerated. We report a case of psychosis induced by exposure to a commonly prescribed drug to treat muscle spasms and associated pain cyclobenzaprine (Flexeril®). Cyclobenzaprine is structurally very similar to tricyclic anti-depressants, such as amitriptyline. While it is well known that agitation caused by cyclobenzaprine is not an uncommon occurrence in the elderly, there have also been sporadic reports of significant psychosis in association with the use of cyclobenzaprine in younger patients. We report a case of reversible mania in a susceptible 44-year-old patient with a lengthy history of mild borderline personality and bipolar disorder. Shortly after being treated with cyclobenzaprine for pain due to a minor injury, this patient exhibited significant signs of mania although these signs were readily reversible upon termination of the treatment with cyclobenzaprine. The patient's severe adverse reaction to this normally innocuous drug adds weight to the notion that there is reason for caution with its prescription for potentially susceptible patient subgroups. Psychopharmacology Bulletin. 2018;48(4):15-19.

CASE HISTORY

Iatrogenic effects of drugs are a major concern in modern medicine. Although cyclobenzaprine is commonly prescribed in primary care for pain relief from skeletal muscle spasms, there have been sporadic reports in the literature that it can induce episodes of mania in susceptible individuals (Beeber & Manning, 1983; Bulbena-Cabre, Dunn, & Swift, 2015; Harsch, 1984; O'Neil, Knudsen, & Bhaskara, 2000; Shprecher, Sloan, & Sederholm, 2013). Here we report such a case of induction of mania following intake of cyclobenzaprine in a patient with mild bipolar disorder.

The chemical structure of cyclobenzaprine is very similar to that of tricyclic antidepressants, and amitriptyline in particular, from which it differs by just a

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single central double bond (Figure 1). Thus, analogous to tricyclic antidepressants, cyclobenzaprine has peripheral and central anti-cholinergic activity and the ability to block synaptic norepinephrine uptake, while it also exhibits anti-histaminic and serotonergic properties (Share, 1978). While these activities of cyclobenzaprine can give rise to common side effects such as drowsiness, dry mouth, and dizziness, there are also several reports in the literature that have linked cyclobenzaprine intake with acute mania in individuals who otherwise exhibit only relatively minor symptoms of psychological disorders (Beeber & Manring, 1983; Bulbena-Cabre et al., 2015; Harsch, 1984; O'Neil et al., 2000; Shprecher et al., 2013). Based on such sporadic cases of mania in association with recent intake of cyclobenzaprine, it has been suggested that, by potentiating norepinephrine, commonly prescribed doses (i.e., 5–10 mg TID) of cyclobenzaprine may induce acute mania or psychosis in subgroups of susceptible individuals (Harsch, 1984).

Here we report the case of a middle-aged woman with mild bipolar disorder who exhibited significant altered neurocognitive functions following a brief period of cyclobenzaprine ingestion for pain relief.

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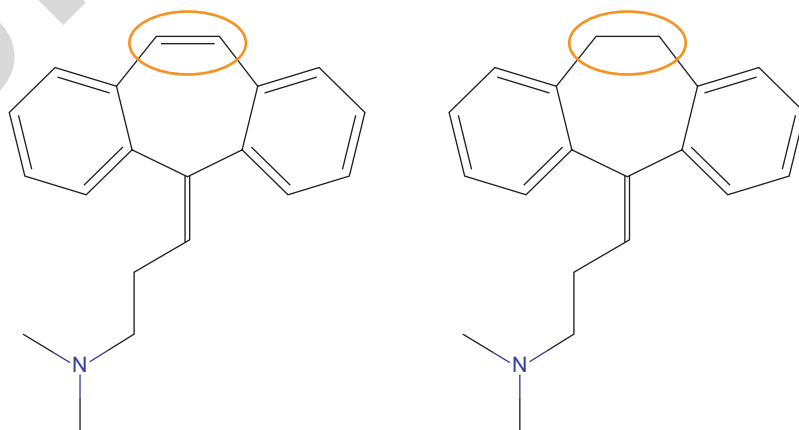
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SYMPTOMATOLOGY

Mrs A, a 43-year-old mother with a lengthy history of depression, alcoholism, and unemployment had made a suicide attempt several years ago that occurred in the aftermath of trauma that she experienced as the result of a home invasion.

FIGURE 1

THE MOLECULAR STRUCTURE OF CYCLOBENZAPRINE (LEFT) AND AMITRIPTILINE (RIGHT), WHICH DIFFER ONLY IN TERMS OF THE DOUBLE BOND IN THE CENTRAL RING OF CYCLOBENZAPRINE



Source: PubChem.org.

She was hospitalised for psychiatric care in the context of another suicide attempt by a deliberate drug overdose. Her initial diagnosis was borderline personality disorder and deliberate drug overdose, and she was referred for outpatient treatment for borderline personality disorder.

One month later Mrs A underwent an outpatient psychiatric evaluation for borderline personality disorder. She was found to be logorrheic and her thought process a flight of ideas, while also exhibiting psychomotor agitation. A diagnosis of non-specific affective disorder was made. Treatment with olanzapine was recommended.

Three months later, she was re-hospitalised for two months. At admission, tachypsychia and a seemingly random thought process were noted. She mainly spoke incoherently and volubly of her purported investigations of instances of collusion and corruption at various levels of government that she claimed to be investigating. Mrs A was diagnosed as having type I bipolar disorder in manic phase, and her discharge treatment was valproate (Epival) and aripiprazole.

Six months later, she was re-examined during an initial consultation at an external clinic. At that time, she was taking her medications as prescribed and she was found to be euthymic. Eight months later, at a second consultation, she was again found to be euthymic, and she stated that she felt at ease and that she was abstaining from alcohol consumption. Her aripiprazole prescription was reduced from 10 mg to 2 mg per day, while the dosing with Epival remained unchanged, at 250 mg in the morning and 750 mg in the evening.

Eleven months later, at a consultation, she complained of insomnia and a degree of anxiety and sadness. Her mood was deemed to be dysphoric and her affect marked by a substantial lability. It was concluded that these symptoms reflected a minimal depressive symptomatology in a bipolar patient. The treatment with aripiprazole was terminated, while divalproex was continued as before.

Thirteen months later, three weeks after having been prescribed cyclobenzaprine at 5 mg TID for pain relief, she urgently required a psychiatric consultation as over the past two weeks she had suffered from insomnia and light-headedness and she was also speaking in a rambling and disjointed manner.

DIAGNOSIS

She was rated as having a score of 9 on the Young Mania Rating Scale, indicating elation without having reached the threshold for mania.

TREATMENT

Her cyclobenzaprine treatment was stopped immediately and aripiprazole was reintroduced.

Fifteen months later, when Mrs A was re-assessed, she was deemed to have regained her baseline functioning and she was rated as having a score of 4 on the Young Mania Rating Scale.

Eighteen months later, at her last documented assessment, she was found to be euthymic and capable of taking care of herself and her young daughter. She was rated as having a score of 6 on the Young Mania Rating Scale and her diagnosis according to DSM-5 criteria was type I bipolar, overall stable.

DISCUSSION

Several cases of psychosis following exposure to cyclobenzaprine have been described in the literature (Beeber & Manning, 1983; Bullena-Cabre et al., 2015; Harsch, 1984; O'Neil et al., 2000; Shprecher et al., 2013). For example, in 1984 Harsch reported two cases involving bipolar patients who exhibited mania within days of having initiated treatment with 10 mg TID cyclobenzaprine for muscle pain resulting from a minor traffic accident. Although both of these patients had previously exhibited manic episodes, they were not regularly taking medication for their manic-depressive illness. These two cases are similar to a more recent report of psychosis following cyclobenzaprine use (O'Neil et al., 2000). This latter case involved an individual with no past psychiatric problems who developed insomnia, decreased appetite, poor concentration, irritability, disorganised thoughts, persecutory delusions, and auditory hallucinations after having started intermittent self-medication with 10 mg of cyclobenzaprine six weeks prior to ease back pain and tension from an injury.

Although these patients required hospitalisation for their induced mania, in all of these cases the psychosis resolved within days of termination of the intake of cyclobenzaprine, often in conjunction with the administration of an antipsychotic agent (e.g., haloperidol or a dibenzoxazepine). The case that we report here also resolved rapidly following termination of the intake of cyclobenzaprine. Notably, in this case, the induced psychosis was not severe enough to warrant hospitalisation. This may have been due to the fact that our patient was already taking medication against bipolar disorder (Epival) at the time that the cyclobenzaprine was initiated. This and the rapid reintroduction of the antipsychotic drug aripiprazole may have prevented a full-blown psychosis.

These documented cases of psychosis following exposure to cyclobenzaprine are reminiscent of prior clinical studies of bipolar patients receiving tricyclic antidepressants (imipramine) versus placebo. Thus, Prien, Klett, and Coffey (1973) found a 67% incidence of mania over 20 months in bipolar patients on imipramine versus a 33% incidence in

a bipolar placebo group. Similarly, in a prospective double-blind study of bipolar patients treated with or without imipramine, Quitkin, Kane, and Rifkin (1981) reported a significantly higher rate of manic relapse for the imipramine-treated group. On the other hand, a study by Lewis and Winokur (1982) did not find an increased frequency of manic episodes in bipolar patients treated with tricyclic antidepressants when compared to a non-treated control group. Although the contradictory findings of these trials are not readily explained, the temporal relationship in the case described here (and in those described by others) between the intake of cyclobenzaprine and the onset on mania clearly indicate that a causal link is highly plausible.

As manic episodes can have quite substantial adverse impacts on the lives of the affected individuals that far outlast the manic episode itself, further investigation of whether exposure to tricyclic drugs increases the frequency of manic episodes is warranted. Moreover, in light of our findings and those of previous case reports (Beeber & Manring, 1983; Bulbena-Cabre et al., 2015; Harsch, 1984; O'Neil et al., 2000; Shprecher et al., 2013), it would also appear to be appropriate at present to consider use of alternatives to cyclobenzaprine for the relief of muscle pain in individuals with known bipolar disorder or other potentially sensitising conditions. ❖

DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare. No financial interests or benefits have arisen from this research and no direct funding was received.

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