Review Article

ISSN: 2230-7346

Journal of Global Trends in Pharmaceutical Sciences

Vol.2, Issue 3, pp -336-349, July -Sept 2011

WITHDRAWAL EFFECTS OF TRICYCLIC ANTIDEPRESSANTS AND THEIR MANAGEMENT

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ABSTRACT

Tricyclic antidepressants (TCAs) including antidepressants from other pharmacological classes are prescribed to treat the depression disorder. These drugs are administered for prolonged period. When the patients show remission after prolonged treatment, the antidepressants administration is discontinued. If the discontinuation is abrupt, it leads to the appearance of a set of symptoms known as discontinuation syndrome or withdrawal reactions. Discontinuation syndrome symptoms are clinically relevant as they cause significant morbidity, and they can also be misdiagnosed leading to inappropriate treatment. Further it can affect patient compliance. Reinstatement of antidepressants leads to the resolution of the withdrawal symptoms. In this article, we have made an attempt to understand the mechanism behind the withdrawal reactions, types of withdrawal symptoms, range of withdrawal reactions associated with different types of tricyclic antidepressants including their management.

KEY WORDS: Antidepressants withdrawal, management of anti depressants withdrawal, Tricyclic anti depressants, Tricyclic anti depressants withdrawal effects.

INTRODUCTION:

Antidepressant drugs are widely used in the treatment of many psychiatric disorders. The decision to discontinue medication after a successful course of treatment, as well as accidental or planned interruptions to treatment, may, in susceptible patients, result in troublesome symptoms which are generally termed "discontinuation". Discontinuation symptoms are now known to be associated with most classes of antidepressants if medication is discontinued without appropriate down-tapering of dose and/or dose frequency.

Symptoms of discontinuation may be mistaken for physical illness, relapse into psychiatric disorder or "addictive" potential of antidepressants.[1] Interruption of treatment with an antidepressant medication is sometimes associated with an antidepressant discontinuation syndrome, in early reports it was referred to as a "withdrawal reaction." Sometimes, the discontinuation of antidepressant therapy is associated with both physical and psychological symptoms. These symptoms are parts of the discontinuation syndrome and are very different from relapse or recurrence. The discontinuation syndrome appears within one week and lasts about three weeks after discontinuation of the antidepressant. In the vast majority of cases, the symptomatology is self-limiting. Sometimes, in the presence of a severe syndrome, reintroduction of the antidepressant induces a rapid resolution of the symptoms. In fact, the discontinuation of the antidepressant should be progressive.[2]

However, the distinction between the discontinuation symptoms and drug withdrawal are clear. Thus, the use of proper terminology when discussing this phenomenon with patients will help to alleviate concerns and stop the spread of common misperceptions. In addition, awareness of the unique nature of discontinuation effects and a grasp of the typical time frame of their emergence can assist in distinguishing between discontinuation syndrome and relapse.[3]Symptoms of antidepressant discontinuation syndrome can include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances and hyperarousal.[4]

Tricyclic antidepressants are the oldest class of antidepressant drugs. They block the reuptake of neurotransmitters such as noradrenaline and serotonin. Toxicity occurs at approximately ten times the normal dosages. These drugs are often lethal in overdoses, as they may cause a fatal arrhythmia. However, tricyclic antidepressants are still used because of

their effectiveness, especially in severe cases of major depression. They include amitriptyline, desipramine, clomipramine, doxepin, protryptiline, imipramine, trimipramine nortryptiline, amoxapine. In non-depressed human subjects, tricyclic antidepressants cause sedation, confusion and motor incoordination. These effects occur also in depressed patients in the first few days of treatment, but tend to wear off in one to two weeks as the antidepressant effect develops. Symptoms related to tricyclic antidepressant withdrawal have been reported to begin immediately or up to forty eight hours after withdrawal, and to continue for as long as fourteen days. The four main syndromes associated with withdrawal of tricyclic medications are gastrointestinal or somatic distress, with or without anxiety and agitation, sleep disturbances, movement disorders and paradoxic activation or mania. These symptoms have been reported to occur in both adults and children. The mental irritability and tachypnea have been occurred in a few infants born to mothers taking tricyclic antidepressants during pregnancy.

Mechanism of Antidepressant Action of TCAs:

The main immediate effect of tricyclic antidepressants is to block the uptake of amines by nerve terminals, by competition for the binding site of the amine transporter. Synthesis of amines, storage in synaptic vesicles, and release are not directly affected, although some TCAs appear to increase transmitter release indirectly by blocking presynaptic α_2-adrenoceptors. Most TCAs inhibit nor-adrenaline and 5-HT uptake by brain synaptosomes to a similar degree but have much less effect on dopamine uptake [5].

Mechanism behind the Withdrawal Effects of TCAs:

Antidepressant discontinuation syndrome occurs in approximately 20 percent of patients after abrupt discontinuation of an antidepressant medication that was taken for at least six weeks.[6] The abrupt discontinuation of antidepressants can result in a syndrome of adverse events, including somatic, mood and psychomotor reactions.[7]

TCAs have anti cholinergic effects, cause excessive blockade of norepinephrine reuptake at the postganglionic synapse, direct alpha adrenergic blockade, and importantly they block sodium membrane channels with slowing of membrane depolarization, thus having quinidine like effects on the myocardium.[8]

Since they affect the cholinergic system, rapid discontinuation occurs which cause signs of Parkinsonism and problems

with may balance. Multiple case reports demonstrate that antidepressant discontinuation syndrome associated with tricyclic antidepressants closely mimics that of the SSRIs. However, signs of parkinsonism and profound problems with balance appear to be especially characteristic of antidepressant discontinuation syndrome caused by tricyclic antidepressants.[9,10]

Antidepressant discontinuation syndrome symptoms caused by tricyclic antidepressants that suggest cholinergic rebound (e.g., parkinsonism and other problems with movement) may respond to short-term use of anticholinergic agents such as atropine or benztropine. This should be considered especially for patients who are opposed to restarting their tricyclic antidepressant. [11] The mechanism for the development of mania or hypomania after withdrawal of antidepressants is not known. Some researchers have proposed that withdrawal of antidepressants can cause "behavioural activation on a continuum to frank mania" due to cholinergic overdrive.[12]

Unwanted Effects with Normal Clinical Dosage:

Tricyclic antidepressants produce a number of troublesome side effects, mainly due to interference with autonomic control. Atropine-like effects include dry mouth, blurred vision, constipation and urinary retention. These effects are strong with amitriptyline but much weaker with desipramine. Postural hypotension occurs with TCAs. This may seem anomalous for drugs that enhance noradrenergic transmission, and possibly results from an effect on adrenergic transmission in the medullary vasomotor centre. The other common side effect is sedation, and the long duration of action means that day time performance is often affected by drowsiness and difficulty in concentrating. Tricyclic antidepressants, particularly in overdose, may cause ventricular dysrhythmias associated with prolongation of the QT interval of electrocardiograph. Usual therapeutic doses of TCAs increase the risk of sudden cardiac death slightly but significantly.[5]

Withdrawal Symptoms Commonly Produced on Discontinuation of TCAs:

The common withdrawal symptoms occur with tricyclic antidepressants include general, gastrointestinal, sleep, balance, movement, affective, dizziness, anxiety, irritability, panic attacks, mood change, decreased concentration, and insomnia. Nausea is occasionally associated with vomiting.[13]

The gastrointestinal symptoms are abdominal pain, nausea, anorexia, vomiting. Somatic symptoms include

sweating, chills, dizziness, lethargy, headaches and flu- like symptoms. Sleep disorders include insomnia, vivid and excessive dreaming. Affective disorders include depressive mood, anxiety, irritability, crying spells and agitation. Balance related symptoms include vertigo, ataxia, parkinsonism and akathisia. Sensory disturbances include numbness, paresthesia and shock like sensations.[14]

Amitriptyline:

Amitriptyline is a tertiary amine tricyclic antidepressant. The manner in which the tricyclic antidepressants exert their clinical antidepressant effect is uncertain but they have been shown to block, in different degrees, the reuptake of various neurotransmitters including serotonin and norepinephrine at the neuronal membrane. This action potentiates the effects of these neurotransmitters.[15] Withdrawal effects of amitriptyline includes aggression, anxiety, balance issues , blurred vision , brain zaps, concentration impairment, constipation, crying spells, depersonalization, diarrhea, dizziness, electric shock sensations, fatigue, flatulence, flu-like symptoms, hallucinations, hostility, highly emotional, indigestion, irritability, impaired speech, insomnia, jumpy nerves, lack of coordination, lethargy, migraine headaches / increased headaches, nausea, nervousness, over-reacting to situations, paranoia, repetitive thoughts or songs, sensory and sleep disturbances, severe internal restlessness (akathasia), stomach cramps, tremors, tinnitus (ear ringing or buzzing), tingling sensations, troubling thoughts, visual hallucinations / illusions, vivid dreams, speech visual changes, worsened depression and mania.[16,17,18]

Clomipramine:

Clomipramine is a tricyclic agent with both antidepressant and antiobsessional properties. A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, fever, insomnia, hyperthermia and irritability. In addition, such patients may experience a worsening of psychiatric status.

While the withdrawal effects of clomipramine have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation.

In most people, these clomipramine withdrawal symptoms improve with time, without the need for any treatment.[19,20,21,22]

Desipramine:

Similar to most other antidepressants, can cause withdrawal effects when use is abruptly discontinued. This withdrawal can affect an individual physically or emotionally. Common withdrawal effects from desipramine are nausea, headache, and malaise. [23, 24, 25]

Doxepin:

Withdrawal effects of doxepin includes aggression, anxiety, balance issues , blurred vision , brain zaps, concentration impairment, constipation, crying spells, depersonalization, diarrhoea, dizziness. electric shock sensations, fatigue, flatulence, flu-like symptoms, hallucinations, hostility, highly emotional, indigestion, irritability, impaired speech, insomnia, jumpy nerves, lack of coordination, lethargy, migraine headaches/increased headaches, nausea, nervousness, over-reacting to situations, paranoia, repetitive thoughts or songs, sensory & sleep disturbances, severe internal restlessness (akathasia),

stomach cramps, tremors, tinnitus (ear ringing or buzzing), tingling sensations, troubling thoughts, visual hallucinations / illusions, vivid dreams, speech visual changes, worsened depression.[26,27]

Imipramine:

A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of imipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of imipramine have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation.[28,29]

Protriptyline:

Withdrawal symptoms can occur if protriptyline is stopped suddenly. The dose should be gradually tapered over several weeks before stop taking it. Symptoms of protriptyline withdrawal can include nausea, headache and malaise.[30]

Management Strategies:

The treatment of discontinuation symptoms depends on

(i) Whether or not further antidepressant medication is warranted and

(ii) The severity of the discontinuation symptoms.

If further antidepressant treatment is warranted, irrespective of the occurrence

of discontinuation symptoms, then restarting the antidepressant will cause rapid resolution of the symptoms. This scenario usually follows failure to take an antidepressant as prescribed, during either the acute or maintenance phase of an illness. If further antidepressant treatment is not clinically indicated then management depends on the severity of the discontinuation symptoms.[31] If antidepressant discontinuation syndrome occurs and other serious causes of these symptoms have been ruled out, the physician should begin by providing reassurance to the patient that the condition is reversible, is not serious or life threatening, and will run its course within one to two weeks. The physician should then consider restarting the antidepressant medication with a slow dose taper or providing support if the patient desires not to restart the antidepressant. Severe symptoms should resolve in fewer than three days, and often within 24 hours. If the antidepressant discontinuation syndrome occurs during a tapering of the antidepressant, consider restarting at the original dose and then taper at a slower rate.[6] Symptoms of gastrointestinal and somatic distress sleep disturbance, and movement disorders and mania have been temporally linked to withdrawal of TCAs. Cholinergic and adrenergic overdrives after TCA discontinuation have been suggested as the proposed mechanism for this syndrome. Reported symptoms may be psychosomatic or related to underlying mental illness.[32] Neonatal discontinuation symptoms can follow maternal use of antidepressants during pregnancy and possibly breast feeding. The patient and doctor must take this into consideration when making prescribing decisions.[33]Because there has been little research on the ideal rates for antidepressant discontinuation, published recommendations for taper rates are often vague. Consequently, the magnitude and speed of the dose reduction are often left to clinical judgment. Some specific recommendations have been reported. For example, Monoamine Oxidase Inhibitors (MAOIs) dosages should not usually be reduced by more than 10% per week, and patients should be monitored carefully TCAs should be reduced with great care over at least 2 to 3 months; if symptoms occur, the dose should be increased and the taper started again at a slower rate. With TCAs, it may be advisable to slow the taper even more near the end of the discontinuation phase.[14]

DISCUSSION:

The terms ‘antidepressant discontinuation symptoms’ and ‘antidepressant withdrawal symptoms’ are used interchangeably in the

literature. The occurrence of withdrawal symptoms does not in itself indicate that a drug causes dependence as defined in ICD–10 (International Classification of Diseases) and DSM–IV (Diagnostic and Statistical Manual of Mental disorders). An extensive report published by the Committee on Safety of Medicines concluded that 'there is no clear evidence that the SSRIs and related antidepressants have a significant dependence liability or show development of a dependence syndrome according to internationally accepted criteria (DSM–IV or ICD–10). The abrupt discontinuation or decrease in the dosage of the intake of medications causes the withdrawal reactions.[34]

Antidepressant discontinuation symptoms affect the patients clinically, socially and therapeutically. Though typically mild, antidepressant discontinuation syndrome symptoms are associated with significant discomfort, work absenteeism, other psychosocial problems, and, may on rare occasions be severe enough to require hospitalization. Failure to recognize antidepressant discontinuation syndrome may result in medical and psychiatric misdiagnosis, potentially exposing patients to unnecessary diagnostic investigations or potentially risky medical interventions. Patients may be unwilling to use psychotropic medications in the future, thereby increasing their vulnerability to future relapses of depressive or anxiety disorders.[6] The discontinuation syndrome associated with tricyclic antidepressants includes both physical and psychological symptoms but are much less likely to be associated with sensory abnormalities and problems with equilibrium.[35] Physical symptoms include lethargy, headache, tremor, sweating, anorexia, insomnia, nausea, vomiting and diarrhea. Psychological symptoms include irritability, anxiety, agitation, low mood, excessive dreaming, nightmares and paradoxical activation. Hypomania, akathisia, parkinsonism, cardiac arrhythmias, panic attacks and delirium have been reported rarely on discontinuation of TCAs.[36]

The TCAs act on different sites. TCAs block the uptake of monoamines such as serotonin and norepinephrine in the CNS. In addition they block variety of receptors like muscarinic, alpha adrenergic, histamine H_1, 5-HT_1, $5HT_2$ and occasionally dopamine D_2. However the relative potencies at these sites differ among different compounds. TCAs inhibit active uptake of biogenic amines NA (noradrenaline) and 5-HT into their respective neurones and potentiate them. Most of the compounds do not inhibit dopamine uptake, except bupropion. However, it has been proposed that TCAs

indirectly facilitate dopaminergic transmission in forebrain that may add to the mood elevating action.[37]

The symptoms of TCA discontinuation, believed to be related in part to an adaptive hypersensitivity of muscarinic cholinergic receptors are called cholinergic rebound or cholinergic overdrive.[14]

TCAs have anticholinergic effects which lead to cause excessive blockade of norepinephrine reuptake at the postganglionic synapse and also cause direct alpha adrenergic blockade. And importantly they block sodium membrane channels with slowing of membrane depolarization, thus, having quinidine like effects on the myocardium. [8]

Antidepressant discontinuation syndrome symptoms caused by tricyclic antidepressants that suggest cholinergic rebound (e.g., parkinsonism and other problems with movement) may respond to short-term use of anticholinergic agents such as atropine or benztropine. Multiple case reports demonstrate that antidepressant discontinuation syndrome associated with tricyclic antidepressants closely mimics that of the SSRIs. However, signs of parkinsonism and profound problems with balance appear to be especially characteristic of antidepressant discontinuation syndrome caused by tricyclic antidepressant discontinuation.

The symptoms of antidepressant discontinuation syndrome that are associated with most antidepressants share features of major depression, including dysphoria, appetite changes, sleep problems, cognitive problems, and fatigue. By focusing on symptoms that distinguish antidepressant discontinuation syndrome from depressive illness relapse (e.g., dizziness, “electric shock” sensations, “rushing” sensations in the head, headache, and nausea) and observing for rapid (i.e., within a few days) reversal of symptoms after restarting the antidepressant or complete resolution of symptoms in one to two weeks (highly uncharacteristic of a depressive relapse), a definitive diagnosis is fairly easy to make.[6]

Long-term administration of TCAs blocks muscarinic cholinergic receptors in the human caudate leading to a compensatory increase in the number of postsynaptic muscarinic receptors (up-regulation) and thus a supersensitivity to muscarinic agonists. Stopping the TCA unmasks this supersensitivity and may also disrupt the cholinergic dopaminergic balance, contributing to the signs of parkinsonism and other balance disturbances that may occur with TCA discontinuation.[14] Thus long-term use of TCAs with potent anticholinergic properties leads to

upregulation of postsynaptic muscarinic receptors, creating a "supersensitive" state.[36]

The discontinuation symptoms of any antidepressants occur shortly after stopping drug or reducing the dose. [13] But the abrupt discontinuation of TCAs can cause cholinergic rebound with symptoms emerging as soon as 12 hours but typically 24 to 48 hours after the last dose.[36]

Maternal use of antidepressants during pregnancy can result in a neonatal discontinuation syndrome characterised by the symptoms such as irritability, respiratory difficulty and poor feeding. Tapering or discontinuing antidepressants prior to delivery may therefore be beneficial for the neonate. But it introduces the risk of depressive relapse in the mother. Neonates born to mothers on antidepressant therapy should be monitored for discontinuation symptoms over the first week of life.[35]

When patients fail to respond to a particular antidepressant, or exhibit side effects, and a trial of another antidepressant is indicated, the clinician must be familiar with the pharmacology of the drug that is being discontinued, the potential for drug-drug interactions, and the time to onset of effectiveness of the new medication.[38]

When attempting to withdraw and stop an antidepressant, severe discontinuation symptoms appear, either during or at the end of a taper, one should consider increasing the antidepressant dose back to the lowest dose that prevented their appearance, and then commencing a slower taper. Some individuals require very gradual tapers to prevent discontinuation symptoms reappearing.[31]

The best approach to the problem is prevention, which involves educating the patients and healthcare professionals about the discontinuation symptoms and ensuring that antidepressants are tapered before they are stopped. When symptoms do occur, reassurance is usually sufficient; in some patients, however, there may be a need for symptomatic treatment, temporary reinstatement of the antidepressant (followed by careful tapering). More research into this common and clinically relevant syndrome is required so that evidence-based recommendations can be developed.[35]

CONCLUSION:

Tricyclic antidepressants are used to treat various psychological disorders. They produce some discontinuation symptoms after abrupt withdrawal. The common withdrawal symptoms of all tricyclic antidepressants include nausea, malaise, headache, sleep disturbance, hyperthermia, irritability,

dizziness, flu-like symptoms, insomnia, imbalance, sensory disturbances, and hyperarousal. Most symptoms are mild and in these cases treatment usually requires only that the patient be reassured about their self-limiting nature. Symptoms can be treated symptomatically if they are of moderate severity. For example insomnia may be treated with a short course of a benzodiazepine. Antimuscarinic agents can help in the treatment of gastrointestinal symptoms following TCA discontinuation, which is consistent with these symptoms being due to cholinergic rebound. If the discontinuation symptoms are severe then the antidepressant can be reinstated, symptoms will usually resolve within 24 h and then the antidepressant can be withdrawn more cautiously. Treatment should always include an appropriate explanation of the symptoms to the patient and follow-up to ensure that the symptoms have resolved.

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