



REVIEW ARTICLE

Caffeine-induced Augmentation of Antidepressant Therapy^{☆,☆☆}

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ARTICLE INFO

Article history:

Received: Apr 12, 2010

Revised: Jul 31, 2010

Accepted: Sep 11, 2010

Available online 23 October 2010

KEY WORDS:

adenosine;
augmentation;
caffeine;
depression;
dopamine

Depressed patients receiving antidepressant treatment for therapeutic purpose also consume caffeine in the form of tea or coffee drinks as a part of their daily life. These depressed patients seek a “lift” because of fatigue or negative affect, thereby consuming high amount of caffeine as a self-medication to increase alertness. This further may lead to increased negative affect and depressive symptoms. Unfortunately, many studies evaluating caffeine in youth have considered samples belonging to either moderate or higher level of caffeine intake. Caffeine, as a psychomotor stimulant, is known to inhibit the pre- and postsynaptic brakes imposed by adenosine on dopaminergic neurotransmission. Evidences also indicate an important role of caffeine as an adenosine receptor blocker in depression treatment. Caffeine may help in the treatment of chronic depression by potentiating dopaminergic system. Antidepressant agents are known to normalize depressed mood by influencing a variety of neurotransmitter systems including dopamine. Evidences suggest a possible positive effect on dopaminergic activity of caffeine augmentation (10 mg/kg or lower dose) with antidepressant agents for depression treatment. These findings suggest a need of considering and future evaluation of possible beneficial effects of low dose of caffeine augmentation with antidepressants in depressed patients.

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1. Introduction

Depression is one of the most common psychiatric disorders and can be very difficult to treat.¹ In recent years, increase in number of prescriptions for antidepressants has been observed. The recently developed drugs act by enhancing the activity of monoamine neurotransmitters, by either reuptake inhibition and enzyme inhibition or activity at pre- or postsynaptic receptors. These newly developed agents have better safety and tolerability over tricyclic antidepressants and monoamine oxidase inhibitors.²

Caffeine is the most widely consumed central nervous system stimulant.³ Epidemiological evidence indicates need of empirical attention toward its use in youth. At least one caffeinated beverage is consumed daily by 75%–98% of youth,^{4,5} whereas consumption of more than two caffeinated beverages was reported in 31% of youth.⁵ Caffeine consumption in youth showed an improved performance

on attention-related tasks. Similarly, a moderate consumption of caffeine showed improved performance and decreased self-reported “sluggishness” in children.⁶ Interestingly, caffeine also plays a cyclical role in affect regulation. Its use may contribute in arousal, anxiety, and irritability, thus exacerbating negative affect states.^{7–9} Its mechanism of action includes mobilization of intracellular calcium and inhibition of specific phosphodiesterases, which occur only at high nonphysiological concentrations of caffeine. The antagonism of endogenous adenosine is important in establishing its central and noncentral effects. Adenosine A₁ and A_{2A} receptors are the preferred targets of caffeine.¹⁰ El Yacoubi et al³ reported prolongation of escape behavior with adenosine A_{2A} receptor antagonists in tail suspension test and forced swim test used for the preclinical evaluation of antidepressant agents. Studies with caffeine have reported activation of noradrenaline neurons and its interaction with the central dopaminergic system. Caffeine mimics and potentiates the behavioral effects of direct or indirect dopamine receptor agonist. Moreover, the action of caffeine on serotonin neurons is similar to other methylxanthines. Apart from these outcomes, reports suggested lesser development of tolerance and withdrawal symptoms with caffeine than other psychostimulants.^{11,12} These findings suggest the importance of consideration of assessment of probable impact of caffeine's consumption in depressed patients.

[☆] Source of funding: Self-funding.

^{☆☆} Conflict of interest: None.

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Use of caffeine as an affect regulator, like cigarettes and other stimulants, is well known. It is widely available with heavy marketing. Its consumption is socially accepted as a stimulant in child and adolescent populations. Caffeine may be particularly appealing to depressed youth seeking a "lift" because of fatigue or negative affect.^{6,13} In support of this view, Bernstein et al¹³ reported elevated self-reported anxious and depressive symptoms in adolescents with caffeine dependence.

Whalen et al¹⁴ assessed youth with depression for their caffeine use and sleep in the natural environments. At baseline, higher caffeine consumption was reported in youth with depression than healthy control. This outcome suggests the probable use of caffeine to help treat symptoms of depression in youth with major depressive disorder before commencement of antidepressant therapy.¹⁴ The lack of energy and chronic tiredness may induce youth with depression for the use of caffeine as a self-medication to increase alertness.^{15,16} Moreover, many youths with depression consume higher amount of caffeine to encounter a period of withdrawal and return to the original state of low energy after the stimulating effect of caffeine.¹⁷ During withdrawal period, this cycle may contribute to increased negative affect and depressive symptoms.¹⁴ Furthermore, Lee et al¹⁸ reported increased sensitivity to caffeine in a few depressed patients. Unfortunately, many studies evaluating caffeine in youth have considered samples belonging to either moderate or higher level of caffeine intake.^{13,19,20} Thus, there is a need to consider a wide range of caffeine dose. In depression-related studies, consideration of lower dose of caffeine may show positive outcomes.

At present, the information on the augmentation effect of antidepressant therapy with various doses of caffeine is lacking. Chronic treatment with antidepressants mainly influences a variety of neurotransmitter systems,²¹ thereby elevating mood levels, while caffeine is also known as a mood elevator through stimulant action.²² In addition to its inhibitory action on adenosine A₁ and A_{2A} receptors, caffeine is also known to increase the neurotransmitter levels.²³ These facts indicate the need of due consideration toward evaluation of caffeine in depression treatment. The objective of this article is to discuss the possible role of caffeine in patients receiving antidepressant therapy and resultant augmentation impact on their psychological status.

2. Adenosine and Depression

The role of adenosine in the central nervous system and peripheral system as an endogenous modulator of synaptic function is well known.²⁴ Among adenosine A₁, A_{2A}, A_{2B}, and A₃ receptors, A₁ and A_{2A} are predominantly expressed in brain.¹¹ As mentioned earlier, caffeine effects are mainly mediated through adenosine A₁ and A_{2A} receptors.¹¹ The latter receptor exhibits lower affinity toward adenosine and stimulates adenylyl cyclase, whereas adenosine A₁ receptor has higher affinity to adenosine and inhibits adenylyl cyclase.²⁴ The striatal localization of adenosine A₁ and A_{2A} receptors negatively affect the motor-activating and reinforcing effects of caffeine. However, localization of adenosine A₁ receptors in the brainstem and basal forebrain and A_{2A} receptors in the hypothalamus is associated with caffeine-induced arousal.¹¹

Adenosine and its analogs have shown to induce "behavioral despair" in animal models believed to be relevant to depression.²⁵ A study showed involvement of adenosine in the effect of antidepressants on glutamate and aspartate release in the rat prefrontal cortex.²⁵ Ongini et al²⁶ have demonstrated a significant improvement in motor dysfunction with A_{2A} receptor blocker SCH 58261. The data published by El Yacoubi et al³ showed reversal of signs of behavioral despair in the tail suspension and forced swim test by selective adenosine A_{2A} receptor antagonists (e.g., SCH

58261, ZM241385, and KW6002). In addition, genetic inactivation of this receptor is also reported as effective. As per Barone and Roberts¹⁰, the adenosine A_{2A} receptor antagonists can be a novel approach in the treatment of depression.¹⁰ Adenosine A_{2A} is one of the preferred targets of caffeine.¹⁰ El Yacoubi et al²⁵ confirmed this hypothesis; however, they reported that a clear-cut antidepressant-like effect could not be ascribed to caffeine. The concomitant administration of adenosine A₁ and A_{2A} receptor agonists showed the synergism of the motor depressant effect.²⁷ Weak or no motor stimulation effect reported with antagonism of adenosine A₁ receptor may be responsible for the synergistic effect along with adenosine A_{2A} receptor blockade.^{28,29} These findings indicate an important role of caffeine as an adenosine receptor blocker in depression treatment.

3. Implications of Dopamine Pathways and Role in Depression

The functional interactions of dopamine and adenosine in the basal ganglia have pathophysiological and therapeutic implications.³⁰ The role of basal ganglia in controlling movement and expression of motivated behaviors is reported by Cauli and Morelli.³¹ The implicated receptors were adenosine A₁ and A_{2A} as well as dopamine D₁ and D₂. Of these, adenosine A₁ receptors are mainly localized in striatopallidal and striatonigral neurons, cholinergic interneurons, dopamine nerve terminal, and glutamate terminals, whereas adenosine A_{2A} receptors are localized only in striatopallidal neurons. Signaling of adenosine A₁ receptor appears to activate G_i family, K channels, and phospholipase C whereas inhibit cyclic adenosine monophosphate and calcium channels. Adenosine A_{2A} and dopamine D₁ receptor appear to signal via G_o rather than G_s proteins.^{30,32–34} Dopamine D₁ receptors are localized in striatonigral neurons, cortical neurons, and D₂ receptors in striatopallidal neurons and dopaminergic neurons. Adenosine A_{2A} receptors appear to play the same role in striatopallidal neurons as dopamine D₁ receptors do in striatonigral neurons.^{30,32–34} Dopamine D₁ and adenosine A_{2A} receptors play a vital role in stimulation of cyclic adenosine monophosphate by dopamine and adenosine in brain.³⁴ The anatomical distribution of adenosine and dopamine receptors and their second messenger level interaction indicate the involvement of dopaminergic system in caffeine-mediated motor effects.³¹ Ferré and Fuxe³⁵ have demonstrated an antagonistic interaction between adenosine A_{2A} and dopamine D₂ receptors in striatal neurons. The activation of dopamine D₂ receptor results in inhibition of adenosine A_{2A} receptor.³⁰ Stimulation of adenosine A_{2A} receptors activates adenylyl cyclase and leads to a reduction of dopamine D₂ receptor signaling. Thus, activation of dopamine D₂ receptor counteracts adenosine A_{2A} receptor signaling.^{30,31,35} Interestingly, this interaction is not merely confined to adenosine A_{2A} and dopamine D₂ receptors.³¹ Ferré et al³⁶ also reported potentiating response induced by dopamine D₁ receptors with adenosine A_{2A} receptor blockade. The ability of caffeine to inhibit the pre- and postsynaptic brakes imposed by adenosine on dopaminergic neurotransmission is considered as its main mechanism in producing psychomotor stimulant activity.¹¹

The field of research has shown a great interest in evaluating role of dopamine in depression. In a chronic stress model, repeated series of minor stresses were given to rats by making changes in their environment. The perturbation of behavior caused by themselves was absent. Outcomes of saccharin solution indicated decreased appetitive (hedonic) drive and activeness in animals. These effects were reversible with standard antidepressants such as tricyclic antidepressants and serotonin reuptake inhibitors. These evidences suggest an implication of dopamine system in fundamental drives such as appetite. The reported decrease in appetite may be because of dopamine receptor subfunction.³⁷ In addition, electroconvulsive

therapy also showed reversal of modeled depression, which is known to increase dopamine in animals and humans.²¹

There are two main dopamine systems that appear to play a complementary role in depression. The first system considers a group of symptoms suggesting psychomotor retardation, which indicate subfunctioning of the substantia nigra basal ganglia motor system. The second parallel system extends from the ventral tegmental area into the ventral striatum (the ventral part of the basal ganglia or the nucleus accumbens) and then up into the prefrontal cortex, which is involved in attention and planning. Unlike norepinephrine and 5-hydroxytryptamine projections, dopamine projections in the frontal cortex are much more localized. Norepinephrine and 5-hydroxytryptamine are present everywhere in brain, whereas dopamine is present only in prefrontal cortex. Dopamine projections in terms of dopamine terminals are low in prefrontal cortex. However, because of higher sensitivity, this system shows large increase in activity than the basal ganglia system in response to stress. In another theory, the correlation of stress leading to the depression is explained. Chronic stress may cause the "burnout" of this system, consequently causing deficiency of dopamine in the region, which may lead to the depression.²¹ D'Aquila et al³⁸ reviewed experimental evidences suggesting a role of dopamine in the mechanism of action of antidepressant drugs. Available outcomes suggested a relation between an increased dopamine D₂-like (i.e., D₂ and D₃) receptor function and a decreased dopamine D₁ receptor number and sensitivity with the increased sensitivity to dopamine receptor stimulation induced by chronic antidepressant treatments. That these changes were prominent in the limbic areas, particularly in the areas innervated by dopamine neurons in the ventral tegmental area, indicate its important role in the therapeutic effect of antidepressant drugs. Furthermore, evidences also suggested an important role in antidepressant mechanism of action because of an enhanced dopamine transmission at the dopamine D₁ receptor level induced by chronic antidepressants.³⁸ D'Aquila et al³⁸ concluded on the probable contribution of potentiation of dopaminergic system in the therapeutic effect of chronic antidepressant treatment.

Depressed patients consuming antidepressant compounds such as serotonergic, noradrenergic, or combined serotonergic and noradrenergic activity may remain symptomatic despite adequate treatment. Development of antidepressant agents with prodopaminergic properties may possess a relatively wide safety margin and improved standard of care for depression. Antidepressant drugs such as monoamine oxidase inhibitors (phenelzine, tranylcypromine, and isocarboxazid); catechol O-methyltransferase inhibitors (tolcapone and entacapone); norepinephrine-dopamine reuptake inhibitors (bupropion); serotonin, norepinephrine, and dopamine-reuptake inhibitors (sibutramine); and selective dopaminergic drugs such as amineptine-dopamine reuptake inhibitors and piribedil, bromocriptine, and pergolide acting on dopaminergic receptors have prodopaminergic activity.³⁹ Similarly, caffeine also produces psychostimulant effect by adenosine inhibition and subsequent enhanced dopaminergic neurotransmission.¹¹ These outcomes suggest a possible positive effect on dopaminergic activity of caffeine augmentation with antidepressant agents in depression treatment.

4. Discussion

Caffeine consumption in psychiatric patients has been analyzed in many trials. Rihs et al⁴⁰ reported higher prevalence of having excessive caffeine intake among psychiatric patients. Leibenluft et al⁴¹ also observed similar outcomes. Their study has demonstrated higher consumption of caffeine in psychiatric volunteers than normal volunteers, particularly in response to the depressive symptoms.⁴¹ Furthermore, heavy coffee drinking (≥ 8 cups/d or

≥ 750 mg/d) was associated with higher risk of suicide compared with more moderate drinkers in Finnish population.⁴² Association between psychosis and moderate to excessive caffeine consumption in psychiatric patients and also in psychiatrically healthy people (only at excess dose) is reported by Broderick and Benjamin.⁴³ In a recent case report, Hedges et al⁴⁴ postulated the correlation between excessive consumption of caffeine and development of psychosis. This study also reported resolving of depression and psychosis condition after lowering caffeine intake without the use of antipsychotic medication.⁴⁴ In preclinical studies, the direct inhibition of caffeine metabolism is reported with antidepressants such as tricyclics, selective serotonin reuptake inhibitors, mirtazapine, and nefazodone when added *in vitro* to liver microsomes.⁴⁵ Indirect inhibition was observed with prolonged administration of sertraline and mirtazapine via inducing CYP1A2 and fluoxetine, sertraline, and mirtazapine via inducing CYP2C. The most effective inhibition of 1-*N*-demethylation is observed with desipramine, sertraline, clomipramine, and imipramine, whereas the most effective repression of 3-*N*-demethylation is observed with imipramine, clomipramine, and desipramine. Desipramine and nefazodone were effective in reducing 7-*N*-demethylation. In addition, inhibition of 8-hydroxylation of caffeine was also reported with fluoxetine, imipramine, and clomipramine.⁴⁵ These preclinical findings may help in understanding the caffeine-induced psychosis, particularly at moderate to higher consumption. However, clinical data are further needed in support of these findings.

Studies evaluating antidepressant properties of caffeine have reported mixed outcomes. Caffeine possessed antidepressant effects in many different animal models of depression.^{25,46,47} However, there are reports with both negative⁴⁸ and positive outcomes^{40,49} associated with depression scores in humans. High caffeine consumption among depressed people may have been a result of self-medication.^{41,50} However, assessment of low to moderate consumption of caffeine (250–400 mg/d) in healthy subjects has shown an increased level of energy and attention, reduced time of reaction, and improved performance in simple cognitive tasks.⁵¹ A recent randomized, double-blind, crossover study assessed 77 low-caffeine users, evaluated the effect of caffeinated coffee on antidepressant-related cooperative behavior, and demonstrated an increased cooperative game

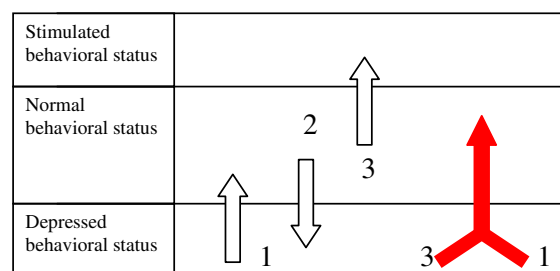


Figure 1 Schematic representation of probable effect of caffeine (10 mg/kg or lower dose) augmentation with antidepressant drugs. 1 = Antidepressants relieve depression by increasing brain monoamine levels.^{55,56} 2 = Caffeine at higher doses is known to cause or worsen depression status and psychosis.^{57–59} 3 = However, consumption of caffeine in lower dose is known to produce stimulant effect.⁶⁰ Combination of 3 and 1 = Hypothesis demonstrating augmentation of caffeine (10 mg/kg or lower dose) with antidepressants in depressed patients may produce beneficial effects.

behavior and sadness communication, resulting in strengthened social support. This further may help in elevating depressive condition.⁵²

As mentioned earlier, unfortunately, many studies have considered caffeine intake belonging to either moderate or higher level.^{19,20} Caffeine consumption in depressed patients remains high because of seeking of "lift" effect.^{6,13} The following facts may be useful in determining the beneficial dose of caffeine in augmentation with antidepressant drugs.

- Ingestion of single cup of coffee delivers a dose of 0.4–2.5 mg/kg.⁵¹
- Denaro et al⁵³ have considered consumption of four or more cups of coffee per day (i.e., 12 mg/kg and above) as a high dose intake in a clinical assessment.
- Higher intake of caffeine (i.e., above 12 mg/kg) has showed reduction in its own clearance rate, particularly through accumulation of paraxanthine.⁵⁴
- Tanskanen et al⁴² have considered consumption of eight or more cups per day or ≥ 750 mg/d of coffee as heavy coffee drinking.

These findings suggest the need of considering lower dose of caffeine (i.e., 10 mg/kg or low) augmentation with antidepressant agents for achieving better therapeutic outcomes in depressed patients (Figure 1).^{55–60} However, there is a need to perform in-detail assessment of low-dose caffeine (10 mg/kg or lower dose) augmentation with each type of antidepressant agents for depression therapy.

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