Abstract

Background: Electroconvulsive therapy (ECT) is a highly efficacious treatment modality used to produce seizures in patients diagnosed with major depressive disorders and psychotic episodes. In general, ECT treatment is successful in most patients; however, in some populations, ECT fails to produce adequate response. Caffeine, theophylline, and aminophylline are documented to augment seizure activity in ECT. By inhibiting adenosine, these medications can improve ECT response rate in a certain patient population. Caffeine and aminophylline have been documented to prolong seizure duration. Theophylline has been shown to improve seizure duration along with decreasing seizure threshold. All of these medications have very minimal side effect profiles. This review will discuss up-to-date evidence on the effects of xanthine derivatives in patients receiving ECT treatment. Methods: A literature review of PubMed and EMBASE was performed for related studies. Results: Eight studies were included in our review. Premedication with caffeine, theophylline, or aminophylline was associated with increased seizure duration in patients suffering from mental disorders and were indicated to manage ECT. Conclusion: Xanthine derivatives prolong seizure duration in patients treated with ECT.

Keywords: Aminophylline, caffeine, electroconvulsive therapy, theophylline

Methods

A literature search of MEDLINE (1946 to June 2020) and EMBASE (1947 to June 2020) was conducted. The following search terms were used: ECT, caffeine, theophylline, and aminophylline. The following modified PICOS-guided eligibility criteria were used:

- **Population**: patients receiving ECT treatment
- **Intervention**: administration of xanthine derivatives (caffeine, theophylline, or aminophylline)
- **Comparison**: placebo or no intervention
- **Outcome**: seizure duration, clinical outcomes, adverse effects
- **Study Design**: randomized controlled trials

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screening was followed to select studies: (1) participants: human adult participants (age ≥18) diagnosed with mental disorders who had received ECT therapy as part of therapeutic management; (2) intervention: not applicable; (3) comparisons: not applicable; (4) outcomes: increase in seizure duration, and clinical benefit and safety outcomes; (5) study design: randomized controlled studies and observational studies. Studies were excluded if they were published in a language other than English or performed on animal participants. Editorials, letters, commentaries, review articles, and studies with duplicate participants were also excluded from the study. Article references were checked manually.

**Results**

Search results using the specified terms yielded a total of 390 citations in PubMed and 183 citations in EMBASE. Some duplicate citations were included in these results and were removed by comparing each result against the prespecified inclusion and exclusion criteria. A summary of the studies included in this review is shown in Table 1.

**Discussion**

A growing body of evidence suggests that caffeine has an important role in prolonging seizure duration in ECT treatment. In a randomized, double-blind, placebo-controlled trial of forty patients diagnosed with major depressive disorders, caffeine pretreatment was associated with increased seizure duration. In contrast, patients who did not receive caffeine pretreatment required significantly increased charges to achieve the necessary seizure duration. In this trial, patients were randomly assigned to two groups: caffeine pretreatment and stimulus intensity dosing. Caffeine was given in the form of intravenous (IV) caffeine sodium benzoate with a starting dose of 242 mg. The IV was given 5 min prior to ECT treatment sessions, and the need for increased stimulus intensity was eliminated.

Another study found that in patients with major depressive disorder, pretreatment with caffeine was associated with significant increases in seizure duration. This open-label study enrolled 21 patients, in which, eight patients received caffeine; however, caffeine dosing protocol was not reported. Compared to noncaffeine-pretreated patients, patients who received caffeine during the ECT treatment course experienced significantly longer seizure duration. Furthermore, patients pretreated with caffeine required significantly fewer ECT treatment sessions to achieve the desired reduction in Hamilton Depression Scale scores. Furthermore, caffeine pretreatment was associated with significant improvement in Hamilton Depression Scale scores.

**Table 1: Summary of included studies**

| Primary                      | Study design               | Number of patients | Medication used          | Endpoint                        | Diagnosis                        | Primary endpoint reported                   |
|------------------------------|----------------------------|--------------------|--------------------------|--------------------------------|----------------------------------|---------------------------------------------|
| Bozymski et al.              | Retrospective chart review | 71                 | Caffeine                 | Seizure duration               | Mainly depression and catatonia   | Increase in seizure duration in caffeine-treated patients \(P<0.0001\) |
| Coffey et al.                | Randomized, double-blind, placebo-controlled | 40 | Caffeine versus stimulus intensity dosing | Seizure duration               | Mainly Major depressive disorder and bipolar disorder | Caffeine was not inferior to stimulus intensity dosing (no \(P\) recorded) |
| Calev et al.                 | Open-label study           | 21                 | Caffeine versus placebo  | Seizure duration and number of ECT session required | Major depressive disorder          | Caffeine-treated patients had fewer session \(P<0.002\); seizure duration was longer in caffeine treated group (no statistical significance reported) |
| McCall et al.               | Randomized, counterbalanced study | 12 | Caffeine                 | Seizure duration and number of ECT session required | Major depression                  | Caffeine-treated patients had significantly longer seizure duration \(P<0.001\); no significant differences in number of ECT session \(P>0.50\) |
| Kelsey et al.                | Retrospective chart review | 14                 | Caffeine                 | Seizure duration               | Major depression                  | Caffeine increased seizure duration (no statistical differences reported) |
| Tzabazis et al.             | Retrospective chart review | 78                 | Theophylline             | Seizure duration               | Severe depression                 | Theophylline prolonged seizure duration \(P<0.001\) |
| Kemp et al.                  | Retrospective chart review | 14                 | Theophylline             | Seizure duration               | Major depression, psychosis, bipolar disorders | Theophylline prolonged seizure duration \(P<0.05\) |
| Stern et al.                 | Prospective open-label     | 14                 | Aminophylline            | Seizure duration               | Affective disorders and psychotic episodes | Aminophylline prolonged seizure duration \(P<0.0008\) |

ECT: Electroconvulsive therapy
In a series of 12 patients with major depressive disorders who were undergoing ECT treatment received 242 mg of caffeine 5 min prior to stimulus initiation during their third and fourth ECT sessions.[8] Pretreatment with caffeine significantly prolonged seizure duration. It is unclear whether such a small sample size was sufficient to detect the differences between caffeine-and placebo-treated groups. In a randomized double-blind placebo-controlled study that included patients with major depressive disorders, participants received 500 mg caffeine sodium benzoate intravenously versus placebo 5 min before ECT stimulus initiation.[7] The small study did not find a significant difference in EEG voltage ratio, heart rate, or seizure regularity.

Kelsey et al. conducted a retrospective study on 14 elderly patients with major depressive disorder.[9] Patients received 500–1500 mg caffeine sodium benzoate intravenously prior to ECT treatment sessions. Caffeine pretreatment was significantly associated with increased seizure duration. A recent retrospective chart review of patients with major depressive disorder (71%), catatonia (19%), and bipolar mania (2.8%) found that administration of caffeine sodium benzoate was associated with significant increases in seizure duration during ECT treatment sessions. Caffeine sodium benzoate was given at the dose of 500 mg just prior to electrical stimulation. Seizure duration was increased by 24% (P < 0.0001) after caffeine administration.

There is a lack of evidence to evaluate caffeine administration in regard to clinical response or effects on seizure threshold.[6,8] In one study, caffeine administration was associated with increased seizure duration in patients receiving ECT treatment, but no differences in ECT treatment sessions were required to achieve the desired clinical outcome (average treatment sessions: 8.2 in caffeine treated group versus 9.4 in stimulus intensity dosing treated group).[10] In addition, another study of 12 patients receiving ECT found no significant differences in convulsive threshold between caffeine-treated group and placebo group (number of stimulus applications was 2.8 in both caffeine and placebo-treated groups). Furthermore, the stimulus charge was comparable between both groups the same (73.5 mC ± 27.3 mC vs. 73.5 mC ± 34.7 mC).[11]

A relatively low number of studies have evaluated the safety profile of administering caffeine to patients undergoing ECT treatment. Most patients tolerated caffeine pretreatment with significant side effects.[6,7,12] Coffey et al. found no significant differences between a caffeine pretreatment group and stimulus intensity dosing group regarding cognitive function (e.g., memory testing and orientation). Furthermore, there were no significant differences in infusion-related anxiety. Caley et al. evaluated the efficacy and safety of caffeine pretreatment in 21 patients. Caffeine pretreatment was associated with improvement in short-term memory. However, no difference was noted in anterograde memory test, which tests the amount of information forgotten from one day to another, or retrograde memory test scores. Among 14 elderly patients with depressive disorder and pretreated with caffeine sodium benzoate (500 mg), this retrospective study noted elevated mean arterial blood pressure and increased heart rate, but without significance differences.[9] Furthermore, there was an increase in maximum rate pressure product among patients pretreated with caffeine. Rate pressure product is a test performed to measure myocardial workload and myocardial oxygenation.[12]

A retrospective chart review study found that pretreatment with 500 mg caffeine sodium benzoate was associated with significant increase in maximum heart rate (mean heart rate = 106.8 bpm in patients without caffeine pretreatment vs. 113.1 bpm in caffeine pretreated group, P = 0.011). However, there was no association in mean arterial pressure between the two groups (131.2 vs. 133 mmHg, P = 0.36). The study reported that four patients discontinued caffeine treatment prematurely: one patient discontinued treatment secondary to increased anxiety, another patient discontinued treatment because of new-onset atrial fibrillation, the third patient discontinued treatment as a result of prolonged EEG seizure activity that resolved after 163 seconds, and the fourth patient developed new-onset chest discomfort without ECG changes.

Some studies suggest that theophylline administration is associated with improvement in seizure duration when given to patients receiving ECT.[10,13] An open-label study was conducted on eight patients receiving ECT, in which oral sustained-release theophylline (200 mg–400 mg) was given 10 h prior to ECT treatment. Theophylline level was on average 3.4 ± 0.7 mg/L after 200 mg, except one patient who had a level of 6.2 mg/L after a 400 mg dose. Theophylline was significantly associated with increased seizure duration in patients who had short seizure episodes prior to theophylline treatment (15–40 s vs. 0–25 s, P < 0.001).[10]

A retrospective chart review of 14 patients with diagnoses of psychotic episodes and/or depressive episodes to evaluate theophylline efficacy was conducted to evaluate theophylline pretreatment and seizure duration.[11] A calculated theophylline loading dose was given to achieve initial plasma theophylline concentration of 10–12 mg/L. Theophylline was administered 1.5 h prior to ECT sessions to achieve the desired level during ECT. The same study found a significant association between theophylline pretreatment and increased seizure duration (P = 0.048). Furthermore, 71% of patients in the study experienced nonabortive seizures (95% confidence interval [CI], 41.9%–91.6%). This finding suggests that theophylline not only can increase seizure duration but also might assist in seizure generation in patients who experience abortive or missed seizure episodes during ECT treatment.

Tzabazis et al. performed a retrospective chart review on 78 patients undergoing ECT, with an average number of 10 ± 6 sessions.[10] These patients received multiple medications prior to or during ECT treatment sessions. The most commonly used medications were etomidate, theophylline, remifentanil, and S-ketamine. Among these medications, and with comparable
numbers of ECT sessions, theophylline was the only medication that significantly increased seizure duration when administered prior to ECT. Other medications (S-ketamine, remifentanil, and thiopental) had no potential effect on seizure duration.

In general, theophylline was well-tolerated without significant side effects. In a previous study, participants received 200–400 mg of oral sustained-release theophylline if seizure duration was considered short. The study found that incidences of adverse effects such as high blood pressure were not significantly different between the theophylline and nontheophylline treated groups. Furthermore, EEG monitoring did not show excessively prolonged seizure duration. Moreover, ECG monitoring did not reveal postictal tachycardia. Kemp et al. found similar results. In this study, 128 ECT treatment sessions were conducted with prior theophylline administration. EEG monitoring did not show prolonged seizure duration more than 120 s. In addition, reposted adverse effects were reported before theophylline initiation.

IV aminophylline 3–5 mg/kg was administrated to 14 medically stable patients with diagnoses of affective disorders or psychotic episodes 10 min prior to ECT sessions. Increased seizure length was associated with aminophylline administration, and this effect was sustained throughout subsequent ECT sessions. In this study, the administration of aminophylline was not associated with intolerable side effects such as anorexia, nausea, or vomiting.

**Conclusion**

A small number of studies suggest that xanthine derivatives can prolong seizure duration in patients undergoing ECT treatment for several mental disorders. However, insufficient randomized clinical trials have been conducted to determine significant differences in adding such medications to ECT management. Future prospective randomized clinical studies are warranted.

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**Conflicts of interest**

There are no conflicts of interest.

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