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Methadone vs. Acetaminophen Codeine plus Clonidine, As Opioid Substitution Scheme: A Pilot Appraisal

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Article Information

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ABSTRACT

INTRODUCTION

Substitution therapy is defined as the administration under medical supervision of a prescribed psychoactive substance – pharmacologically related to the one producing dependence – to people with substance dependence, for achieving defined treatment aims. Objective of the present evaluation was a comparison between methadone and acetaminophen codeine plus clonidine about management of opioid withdrawal symptoms in a group of non-western inpatient population.

Methods

All patients of an acute division of a public psychiatric hospital, who met dual diagnosis of primary psychiatric disorder plus opioid use disorder, were nominated as accessible sample of the present assessment. Period of estimation was about elven months and the appraisal was accomplished according to a single-blind design. Among 96 patients, cases, who had been prescribed methadone, before the recent admission in hospital, continued the said substitution treatment in line with the recommended dose and preparation till discharge (n = 42). The remaining patients, had been given acetaminophen codeine plus clonidine, as substitution treatment, during their inpatient management (n = 54). The said drugs were prescribed along with the current psychotropic medications. The primary outcome measures included: the 'Cross-Cutting Symptom Measure' and the 'Subjective Opiate Withdrawal Scale', which were scored at baseline, week 1 and week 2, by the same associate clinical psychiatrist, who was unaware regarding the planned procedures.

Results

As said by the outcomes, the mean total score of primary outcome measures reduced meaningfully in both groups at the end of assessment in comparison with the starting point. Moreover, the between-group analysis did not display any significant difference between them in a head-to-head analysis. The Cohen's effect size, too, presented large enhancement in both groups. Furthermore, while QTc interval was elongated by methadone and acetaminophen plus clonidine, no substantial variation in inter-group analysis or between-group analysis was clear after two weeks of management.

CONCLUSION: In line with the outcomes, acetaminophen codeine plus clonidine was, almost, comparable to methadone, in management of clinical and withdrawal symptoms of patients

with opioid dependence.

KEY WORDS: substance abuse; opioid dependence; detoxification; methadone; clonidine; acetaminophen codeine; pharmacologic treatment;

INTRODUCTION:

The three opioid receptors (mu, delta and kappa receptors) mediate activities of both exogenous opioids (medicines) and endogenous opioid peptides, and characterize the key actors in the comprehension of opioid-controlled behaviors [1]. Opioid receptors belong to the superfamily of G protein-coupled receptors. Agonist binding to these receptors ultimately causes inhibition of neuronal activity [1]. Opioid peptides are involved in a variety of functions regulating stress responses, feeding, mood, learning, memory, and immune functions [2]. With repeated administration of opioid drugs, tolerance develops, and higher doses of the medications are necessary to gain the wanted effect [3]. While the existent data display complex and broad changes of the endogenous opioid system following repeated stimulation of mu receptors by opioids, the exact values of those alterations remain indistinct. Anyhow, it is probable that the enduring dysregulation of the opioid system impacts stress responses and drug-taking activities [4]. Symptom severity of opioid withdrawal is associated to the specific narcotic used; amount used; duration of use; and setting factors [5]. Withdrawal phenomena are generally the opposite of acute agonist effects, and people differ markedly, both as to which symptoms are present and their severity [6]. Substitution therapy is defined as the administration under medical direction of a prescribed psychoactive substance, which is pharmacologically related to the one producing dependence, to persons with substance dependence, for attaining defined treatment goals. Substitution therapy is commonly used in the management of opioid dependence and is often referred to as "opioid substitution treatment," "opioid pharmacotherapy", or "opioid replacement therapy" [7]. The mechanisms of action of opioid substitution therapy include prevention of disruption of molecular, cellular and physiological events and, in fact, normalization of those functions already disrupted by chronic use of opiates [8]. Since 1970, methadone maintenance treatment has grown substantially to become the dominant form of opioid substitution treatment globally [9]. Though opioid dependence has more treatment agents accessible than other abused medications, none are curative. They can, however, significantly reduce withdrawal symptoms and craving, and block opioid effects. The most effective withdrawal method is substituting and tapering methadone or buprenorphine. α2- adrenergic agents, as well, can ameliorate untreated symptoms or substitute for agonists if not available [10]. Methadone is orally effective and produces smoother withdrawal. It is safe, if care is taken with initial dosing [10]. Methadone is a long-acting agent, and is excreted primarily in the urine

and is an agonist at μ and δ opiate receptors. It is primarily metabolized through cytochrome P450 (CYP) enzymes, predominantly involving the CYP3A4 pathway [11, 12]. Effects are more likely early in treatment before plasma levels have stabilized [13]. Also, the Food and Drug administration (FDA) approved sublingual buprenorphine in 2002 for office-based treatment for detoxification or maintenance of opioid dependence. Buprenorphine is long-acting, safe, and effective by the sublingual route, but may precipitate withdrawal symptoms if given too soon after an opioid agonist [14]. Clonidine, an antihypertensive drug and α2-adrenergic agonist preparation, as well, has been used to help opioid withdrawal in both inpatient and outpatient settings for over 25 years [15, 16]. It works by binding to α2 auto receptors in the locus coeruleus and suppressing its hyperactivity during withdrawal. While doses of 0.4 to 1.2 mg/day or higher reduce many of the autonomic components of the opioid withdrawal syndrome, symptoms such as restlessness, lethargy, insomnia, and muscle aches may not be satisfactorily controlled [17]. Compared with methadone-aided withdrawal, clonidine has more side effects, especially hypotension, but is less likely to lead to post-withdrawal rebound [10]. Objective of the present evaluation was a comparison between methadone and acetaminophen codeine plus clonidine about management of opioid withdrawal symptoms in a group of non-western inpatient population.

Methods:

Among the separate divisions of a public psychiatric hospital, one of its male sectors was designated as the specific field of investigation. For evaluation, all acute psychiatric inpatients who meet dual diagnosis of primary psychiatric disorder plus opioid use disorder; had been selected as accessible sample. Psychiatric diagnosis was according to the 'Diagnostic and Statistical Manual of Mental Disorders', 5th edition criteria (DSM-5) [18]. Duration of assessment was around eleven months (July 2018 – June 2019) and the evaluation was performed according to a single-blind plan. So, the assessor, who was an associate psychiatrist, was completely unaware about the prescribed medications. While this study was carried out consistent with the 'Declaration of Helsinki and Ethical Principles for Medical Research Involving Human Subjects' [19], the patients were informed about the procedure, and a signed informed consent was received from those who were interested in participating in the study. Substance abuse had been diagnosed by the routine urine toxicology test, which was performed before admission and its result was positive for opioid drugs in individuals with opioid use disorder. In the course of assessment, among 211 admitted psychiatric patients, 121 patients (54.34%) were substance abuser, too (whether opioid, cocaine, stimulant, alcohol or a combination of them). Among them, 108 patients were primarily opioid abuser, who had routinely abused opioid, independently,

or along with other available substances. Twelve patients withdrew soon and released from the hospital according to personal reasons. Among the remaining patients (n=96), and in addition to the current psychotropic medications, individuals who were prescribed methadone, according to printed instructions that had been signed by authentic physicians, in advance of the recent admission in hospital, were allowed to continue their substitution treatment according to the recommended dosage and formulation till release (n = 42). The remaining group of patients received acetaminophen codeine (acetaminophen = 325 mg, and codeine phosphate = 15 mg) plus clonidine (tablet=0.2 mg), as substitution treatment, during their inpatient management (n = 54). The starting dose of acetaminophen codeine was 1 tablet three times per day, which could be elevated to two tablets every eight hours, if necessary. After settle down, acetaminophen codeine was tapered flexibly by one tablet every 3 days, or more slowly, according to situation. The starting dose of clonidine was 0.1- 0.2 mg every eight hours, which could be given if the systolic blood pressure was ≥ 10 mg Hg. After relax, and in consort with tapering of acetaminophen codeine, clonidine was tapered flexibly by 0.1 mg every five days, which in the long run would be terminated after ending of the acetaminophen codeine. The primary outcome measures in the current assessment included the 'Cross-Cutting Symptom Measure (CCSM)' (18) and the 'Subjective Opiate Withdrawal Scale (SOWS)' [20]. The CCSM is a patient- or informant-rated measure that assesses mental health domains that are important across psychiatric diagnoses. It is intended to help clinicians identify more areas of inquiry that may have significant impact on the individual's treatment and prognosis. In addition, the measure may be used to track changes in the individual's symptom presentation over time. The adult version of the measure consists of 23 questions that assess 13 psychiatric domains, including depression, anger, mania, anxiety, somatic symptoms, suicidal ideation, psychosis, sleep problems, memory, repetitive thoughts and behaviors, dissociation, personality functioning, and substance use. Each domain consists of one to three questions [18]. The SOWS, also, is a patient- or informant-rated measure that assesses withdrawal symptoms from opioids and tracking their changes over time. It consists of 16 questions with respect to typical opioid withdrawal symptoms [20]. In the present evaluation, the primary outcome measures had been scored at baseline, week 1 and week 2, by the same associate clinical psychiatrist, who was unaware respecting the planned protocols.

STATISTICAL ANALYSIS

Patients were compared on baseline characteristics by independent samples t-test. treatment effectiveness, as well, which had been assessed by CCSM and SOWS, had been analyzed by independent samples t-test and repeated measures analysis of variance (ANOVA), for intra-group analysis, and Split-plot (mixed) design ANOVA, for between-group analysis. Also, Cohen's effect size (ES'), for measurement of the strength of effectiveness, and power of the study (Post-hoc), for evaluation of Type II error, had been analyzed. Statistical significance was defined as p value ≤ 0.05. MedCalc Statistical Software version 15.2 was used as statistical software tool for analysis.

RESULTS

Analysis for efficacy was based on data from comparable amount patients in both groups (z = 1.73, p ≤ 0.08, CI 95%: -0.26, 0.01), with similar demographic and diagnostic variables (Table 1). Relatively, 20%, 10%, 20%, 10% and 40% of cases met diagnosis of schizophrenia, bipolar disorder, depression, PTSD, and personality disorders, respectively. Intra-group analysis showed that the mean total score of CCSM and SOWS decreased significantly in both groups at the end of trial in comparison with the baseline [(t = 2.47, p ≤ 0.01, CI 95%: 0.84, 7.73), and (t = 3.976, p ≤ 0.0002, CI 95%: 3.45, 10.35), for methadone, and (t = 3.17, p ≤0.002, CI 95%: 1.37, 5.94), and (t = 7.227, p ≤ 0.0000, CI 95%: 5.23, 9.19), for acetaminophen codeine plus clonidine, about CCSM and SOWS, respectively] (Figure 1 and 2). Repeated measures analysis of variance (ANOVA), as well, showed significant changes in both groups with respect to the CCSM [$F_{(2,106)} = 23.6$, p<0.0000, SS=439.86 MSe=9.33, and $F_{(2, 82)} = 7.80$ p<0.007, SS=3117.36 MSe=399.66, for acetaminophen codeine plus clonidine and methadone, respectively] and SOWS [$F_{(2,106)} = 31.08$, p<0.0003, SS=316.75 MSe=8.94, and $F_{(2, 82)} = 6.89$ p<0.001, SS=2903.48 MSe=261.82, for acetaminophen codeine plus clonidine, and methadone, respectively] in the 2nd week. On the other hand, the between-group analysis did not show any significant difference between these two groups in the baseline, the first week and the second week (Figure 1 and 2), which was exposed again by Split-plot (mixed) design ANOVA [$F_{(2,94)} = 0.144$ p<0.866, SS=2.17 MSe=7.55, and $F_{(2,94)} = 0.237$ p<0.138, SS=3.22 MSe=8.70, on CCSM and SOWS, respectively, in the second week]. Since the sample size was small, the Cohen's effect size (ES') was analyzed regarding changes of outcome measures at the end of trial, which showed large improvement in both groups [(Cohen's d=1.39, effect-size r=0.57), and (Cohen's d=0.86, effect-size r=0.39), with respect to CCSM, and (Cohen's d= 0.96, effect-size r= 0.43), and (Cohen's d= 1.13, effect-size r= 0.49), with respect to SOWS, for acetaminophen codeine plus clonidine, and methadone, respectively]. Post-hoc power analysis showed an appropriate power of 0.77 (Critical t<94> = 1.66, Delta = 2.43) for the present assessment, which changed to power = 0.88 in the frame of Compromise power analysis (n1=42, n2=54, Critical t<94> = 1.22, Delta = 2.44). Also, while QTc interval was prolonged from 0.41+/-0.08 to 0.42+/-0.01 and 0.40+/-0.07 to 0.41+/-

0.06, by methadone and acetaminophen clonidine, respectively, no significant alteration in inter-group analysis [(t= -0.804, p ≤ 0.423, CI 95%: -0.03, 0.01) and (t= 1.067, p ≤ 0.288, CI 95%: -0.01, 0.03), for methadone and acetaminophen clonidine, re-spectively]or between-group analysis (t= 0.652, p ≤ 0.5159, CI 95%: -0.02, 0.04) and (t= 1.067, p ≤ 0.288, CI 95%: -0.01, 0.03), in baseline and week 2, respectively] was clear after two weeks of management.

Table1: Demographic profile of participants.

Demographic Variables	Acetaminophen codeine + clonidine (n=54)	Methadone (n=42)	T	P	CI
Gender (male)	100%	100%	-	-	-
Age (years); mean (SD)	31.27±5.81	29.68±6.34	1.27	0.2	-0.88, 4.06
Duration of illness (years); mean (SD)	6.24±3.66	7.45±2.53	-1.82	0.07	-2.52, 0.10
Baseline CCSM	26.19±6.30	24.50±9.52	1.04	0.3	-1.53, 4.90
Baseline SOWS	30.31±10.54	28.85±9.42	0.705	0.4826	-2.65, 5.57

Abbreviations: CCSM = Cross-Cutting Symptom Measure; SOWS = Subjective Opiate Withdrawal Scale.
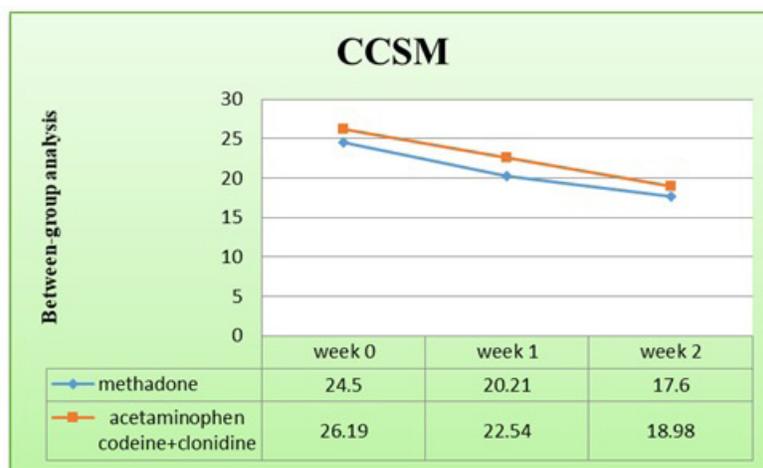
Figure 1: Analysis did not show any significant difference between two groups regarding changes of Cross-Cutting Symptom Measure.
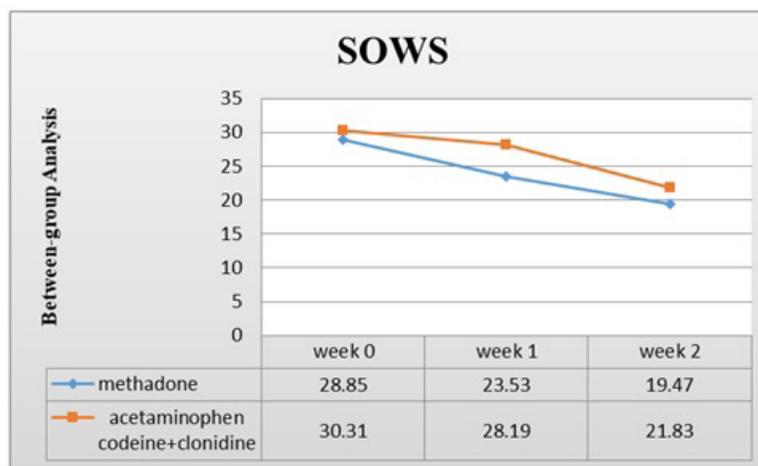
Figure 2: Analysis did not show any significant difference between two groups regarding changes of Subjective Opiate Withdrawal Scale.

DISCUSSION

While compared with other drugs of abuse, opioid dependence benefits from a broader range of accessible pharmacological appa-ratuses for treatment [11], numerous studies have confirmed that methadone maintenance of opioid addicts significantly reduces criminal activity, illicit opioid use, mortality, morbidity, and the risk of new human immunodeficiency virus (HIV) infection, par-ticularly when used with enhanced supplementary services [21, 22, and 23]. Though methadone's plasma half-life, once stabi-lized, averages 24 to 36 hours with a range of 13 to 50 hours, making it a useful once-daily maintenance medication compared with morphine or heroin, individual differences in rate of metab-

olism may produce complaints of withdrawal symptoms, even in those on a stable dose [24]. Anyhow, doses of 30 to 40 mg of methadone usually prevent most withdrawal symptoms and craving [25]. On the other hand, there is high prevalence of co-morbid psychiatric and substance abuse ailments among opioid addicts [26]. So, methadone programs need to screen and refer patients for medical treatment, along with providing or referring for psychiatric illnesses if patients are to passably recover (10). Though methadone is just a medication and not a treatment [27], some randomized studies have suggested that methadone alone is better than being on a waiting list [28]. Back to our discussion and according to the results, while with respect to the primary outcome measures a significant improvement was clear in both groups, no significant difference was palpable between them at the end of trial. Such a finding is in agreement with the findings of Mattick et al. [29], Amato et al. [30], and Nielsen et al. [31], with regard to methadone, as an effective maintenance treatment of opioid dependence by retaining patients in treatment and decreasing opioid use more than non-opioid based replacement therapy, and Renner et al. [32], Strain et al. [33], and Collins et al. [34], with reference to clonidine, for reduction of autonomic symptoms of rapid opioid withdrawal, and Oliva et al. [35], about opioid agonist, for management of opioid withdrawal symptoms and the associated subjective sensations. But about the risk of death during opiate substitution treatment, while our finding was not in harmony with the findings of Gao L et al. [36] Cornish R et al. [37], Krantz et al. [38], Kornick et al. [39], Martell et al. [40], Mayet et al. [41], and Pani et al. [42], due to lack of serious cardiac catastrophes during the present evaluation, persevering cautionary care is a necessary need. Moreover, there was not any significant alteration in QTc in intra-group and between-group analysis. Nonetheless, by taking into consideration the possibility of methadone induced QTc interval prolongation [36] and torsade de pointes [39, 41], which necessitates the QTc interval screening for cardiac risk in methadone treatment of opioid dependence, prescription of more innocent medications, like codeine or clonidine, which has yet no report similar to the impact of methadone on cardiac conduction in opiate users, particularly in cases with intraventricular conduction defects, looks a better strategy. Anyhow, beyond the high risk of fatal respiratory depression, while methadone is associated with prolongation of the electrocardiographic QT interval, the link to cardiac dysrhythmia and sudden cardiac death remains an open question [43]. Indeed, recent studies did not confirm the role of methadone in sudden cardiac death as it was before suspected [44]. On the other hand, acetaminophen codeine and clonidine are cheaper and more accessible in developing countries, than methadone, which is a controlled drug and more expensive than the aforesaid medications, and is available only in clinics specified for treatment of addiction. Also, methadone is a drug with a high

dependency potential and a low lethal dose, which is more potent than opium and other opioids, and may generate its own process of abuse and addiction; a risk, which is less notable with respect to other comparable prescriptions. Essentially, it is undeniable that the methadone and buprenorphine have brought a real benefit in the opioid addiction treatments and have reduced remarkably the death by overdoses and the transmission of blood-borne diseases. They were also shown to keep immune and memory functions, have positive effects on psychopathology and reduction of poly-abuse [45]. However, like any other medications, they are not fully effective as many patients under OST might still relapse [46, 47], and because they are μ- receptor agonist they may be misused [48]. In addition to methadone, the promised safety of buprenorphine was challenged as soon it arrived on the market and for example in France, several death cases were reported where buprenorphine was diverted (intravenous use) [49]. More recently, when gabapentin was used with opioids, there was a substantial increase in the risk of opioid-related death [50]. Moreover, many side effects have been reported with these OST such as a decrease of cognitive performance or sexual dysfunction in men [51]. In rodents, a short treatment (5 days) with buprenorphine or methadone is able to induce behavioral and neurochemical changes until 35 days after withdrawal. so, it looks necessary to find new μ-receptor agonists, or new combinations of μ- receptor agonists and other ligands, that would not induce the neuro-adaptations responsible for the harmful effects of opioids (e.g., addiction, respiratory depression), and would therefore gradually restore homeostasis, thus allowing for instance a complete escape from addiction [52].

The "opioid crisis" dramatically exposes the need for more research in at least two main directions. One is to find better opioid analgesics with less and even almost no addictive potential. The other direction is the discovery of new medications to treat opioid addiction. Regarding the treatment of opioid addiction, no real progress was evident since the introduction of methadone and buprenorphine and most of the current research consists of work related to these compounds or other marketed opioids such as modifying the formulation to get slow release compounds [9]. While the most evidence-based treatment for opioid dependence is opioid agonist maintenance treatment, there are some critical, yet unaddressed issues of OST, especially in the developing countries. These comprise of generalizability of the evidence for OST, especially for natural and pharmaceutical opioids and for all age groups, optimum dose and duration of OST, and mode of treatment delivery including the frequency of dispensing. So, instead of direct copying from Western models, it is important to try to understand the useful and safe program and policy options that are proper for developing societies, with their own assets as well as vulnerabilities [53]. So, while these findings are potentially important, further research should be conducted to properly account

for potential confounding and choice bias in comparisons of side effects and mortality risk between opioid substitution treatments, as well as throughout periods in and out of each treatment [54]. Substance dependence is a complex disorder with biological mechanisms affecting the brain and its capacity to control substance use. It is not only determined by biological and genetic factors, but psychological, social, cultural and environmental factors as well. Currently, there are no means of identifying those who will become dependent, either before or after they start using drugs. So, substance dependence is a medical disorder that could affect any human being. Hence, in view of its comorbidity with other mental or medical illnesses, assessment, treatment and research would be most effective if an integrated approach were adopted. Besides, investments in neuroscience research must continue and expand to include investments in social science, prevention, treatment and policy research, since reduction in the burden from substance use and related disorders must rely on evidence-based policies and programs which are the result of research and its application [9]. Small sample size, short duration of assessment, restriction of study to one academic center, and lack of placebo arm were among the weaknesses of the current evaluation. No doubt, more systematic comparative studies will help to choose better and safer policies with respect to available substitutive strategies.

CONCLUSIONS

In line with the outcomes, acetaminophen codeine plus clonidine was, almost, comparable to methadone, in management of clinical and withdrawal symptoms of patients with opioid dependence.

ACKNOWLEDGEMENTS

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