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Theory and Practice of Treatment of Concurrent Major Depressive and Alcohol Use Disorders: 7 Lessons from Clinical Practice and Research

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ABSTRACT

Objectives: Both major depression and alcohol use are highly prevalent in the Canadian population. They are the major contributors to disability and decreased quality of life and, as they are often comorbid with each other, the diagnosis and treatment of concurrent depression and alcohol use disorder represent a challenging task with multiple clinical questions requiring evidence-based recommendations.
Thus, the goal of this article is to review the optimal strategies to treat concurrent alcohol use and major depressive disorders in the context of current research findings and clinical practice.

Methods: Narrative review, knowledge synthesis, and secondary data analysis.

Results: Based on the review of the relevant literature and secondary data analyses of our own clinical data, we devised a set of pragmatic clinical recommendations and guidance on differential diagnosis between alcohol-induced mood disorder and independent major depressive disorder concurrent with alcohol use disorder, the choice and timing of pharmacological agents, organization of care, selection of best-evidence psychotherapeutic approaches and their integration into clinical practice, management of patients' and team expectations in terms of clinical outcomes, as well as the implementation of measurement-based approaches to optimize care delivery and achieve better clinical outcomes.

Conclusions: Seven clinically relevant problems were reviewed and the evidence-based ready-to-implement clinical approaches were offered.

Keywords: alcohol use disorder, concurrent disorders, integrated care, major depressive disorder, measurement-based care

Objectifs: La dépression majeure et la consommation d'alcool sont très répandues dans la population canadienne. Ils sont les principaux contributeurs à l'invalidité et à la diminution de la qualité de vie et, comme ils sont souvent comorbides les uns avec les autres, le diagnostic et le traitement de la dépression concomitante et des troubles liés à la consommation d'alcool représentent une tâche difficile avec de multiples questions cliniques nécessitant des recommandations fondées sur des preuves. Ainsi, le but de cet article est d'examiner les stratégies optimales pour traiter la consommation concomitante d'alcool et les troubles dépressifs majeurs dans le contexte des résultats de recherche actuels et de la pratique clinique.

Méthodes: Revue narrative, synthèse des connaissances, analyse des données secondaires.

Résultats: Sur la base de la revue de la littérature pertinente et des analyses de données secondaires de nos propres données cliniques, nous avons conçu un ensemble de recommandations cliniques pragmatiques et de conseils sur le diagnostic différentiel entre les troubles de l'humeur induits par l'alcool et les troubles dépressifs majeurs indépendants concomitants avec les troubles liés à la consommation d'alcool, le choix et le timing des agents pharmacologiques, l'organisation des soins, la sélection des approches psychothérapeutiques les plus probantes et leur intégration dans la pratique clinique, la gestion des attentes des patients et des équipes en terme de résultats cliniques ainsi que la mise en œuvre d'approches basées sur la mesure afin d'optimiser la prestation des soins et obtenir de meilleurs résultats cliniques.

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DOI: 10.1097/CXA.0000000000000125

Conclusions: Sept problèmes cliniquement pertinents ont été examinés et des approches cliniques fondées sur des preuves prêtes à être mises en œuvre ont été proposées.

Mots clés: soins fondés sur des mesures, soins intégrés, trouble dépressif majeur, trouble lié à la consommation d'alcool, troubles concomitants

INTRODUCTION

Alcohol use disorder (AUD) is a highly prevalent, chronic, relapsing condition associated with multiple medical and psychiatric comorbidities, disability burden, and high societal costs.[1,2] According to the 2012 Canadian Community Health Survey[3] the lifetime and annual prevalence of AUD in Canada is 18.1% and 3.2%, respectively. The estimated socioeconomic burden associated with AUD represents 37% of the costs associated with all substances of abuse ($40 billion in 2002).[2] One of the major psychiatric comorbidities of AUD is major depressive disorder (MDD),[4–6] which in turn is also highly prevalent in the Canadian population with the lifetime and annual prevalence of 11.3% and 4.7%, respectively.[7] Along with AUD, depression is the major contributor to morbidity, mortality, and socioeconomic burden.[8] Both conditions have a high degree of comorbidity—prevalence of each disorder is more than twice higher in subpopulations with another disorder when compared to the general population.[9,10] When concurrent, AUD and MDD are associated with an even higher degree of disability, reciprocal aggravation of each other's course and prognosis, and significant difficulties in treatment planning.[4,11]

Despite significant attention turned toward concurrent disorders in the past decades[12,13] and even with the most recent systematic reviews and guidelines for the treatment of these conditions,[14,15] a wide range of clinical questions remain either unclear or unanswered. Specifically, further guidance is often necessary for the areas of differential diagnosis, the rationale for selection and timing of the use of antidepressants and antidipsotropic medications, sequencing of treatment modalities as well as care organization, clinician and patient expectations, and the use of measurement-based care paradigm.

Thus, the goal of this article is to provide the readers with up-to-date clarification on these issues based on the review of scientific literature and the clinical data derived from the extensive clinical and administrative practice.[16–19]

Differential diagnosis between major depressive and alcohol-induced mood disorders

It is widely accepted that a proper treatment plan starts with diagnosis, which in turn requires diligent differential diagnosis.[20] In the case of concurrent AUD and major depression, one of the biggest clinical conundrums is the proper differentiation between the co-occurring, independent MDD, and alcohol-induced mood disorder as the treatment approaches would significantly differ.[12]

Careful examination of the timeline of the development of both disorders is a highly efficient method of establishing or discarding the possible causal relationship. Suggestions for the differential diagnosis based on various sources[6,21–24] are summarized in Table 1.

Based on clinical experience,[25] it is often (in 30%–40% of cases) impossible to differentiate between alcohol-induced and primary depressive episodes with a high degree of certainty due to a variety of reasons—lack of

Table 1: Differential Diagnosis between Alcohol-Induced Mood Disorder and Independent, Concurrent, and Major Depressive Disorder

Criterion	Independent, concurrent major depressive disorder/episode	Alcohol-induced mood disorder/major depressive episode
Time of onset	Precedes or independent of the onset of alcohol consumption	Follows the onset of heavy drinking or heavy drinking episodes
Recurrent major depressive episodes	Occur without any temporal association with alcohol consumption	Often follow the periods of heavy drinking and/or emerge around the time of heavy alcohol use
Remission	Independent or even despite ongoing alcohol use	Often spontaneous and co-occurs with cessation or reduction in alcohol use
Periods of sobriety	Have little or no effect on depressive symptomatology	Depressive symptomatology tends to significantly improve
Severity	No correlation with the drinking severity, but may correlate with other patient characteristics such as sex, age, illness duration, adverse life events, and stressors	Tends to correlate with the duration and severity of alcohol use disorder and drinking frequency and amounts of alcohol consumed
Actuarial data	More likely to occur in married, Caucasian, females, history of suicide attempts, and family history of mood disorders	More likely to have other addictions and a history of prior treatment for alcohol use disorder

collateral information, patient's inability to recall crucial elements of the symptoms development timeline, treatments received, alcohol consumption patterns or, ultimately, the presence of multiple depressive episodes of apparently mixed etiology. In such cases, another clinical question arises—should antidepressants be initiated immediately or after a period of abstinence?

Antidepressants—when to start? (and whether to start or not)

Choosing Wisely Canada[26] recommendation is to first consider the possibility of a period of sobriety and subsequent reassessment for the persistence of depressive symptoms, which at least in theory would allow for a) complete differentiation between alcohol-induced mood disorder and concurrent MDD, b) assessment of the severity of independent mood disturbances, and c) better treatment compliance when abstinent. While this recommendation appears to be logically sound and reasonable, there are quite a few counter-arguments to this proposition.[27]

First of all, the effectiveness of treatment of AUD tends to be quite low even in cases of patients with only 1 diagnosis —recent meta-analysis yielded a small, but significant effect size and the number needed to treat for naltrexone and acamprosate of 7.5 and 8.6, respectively[28] and it tends to be even lower in depressed patients with AUD who tend not to adhere to antidipsotropic medications and to show even poorer response to treatment protocols.[18] Additionally, the etiology of depressive episodes may be unclear in many cases and, as longitudinal studies show, a significant portion of apparently alcohol-induced depressive episodes are being later reclassified into independent ones.[29] Also, there is an indication that early use of antidepressants in patients with addictions often results in fast and significant responses.[30]

Ultimately, there is limited, but illustrative evidence of higher effectiveness of combination therapy with an antidipsotropic medication (naltrexone) and an antidepressant as opposed to naltrexone alone. The study of Pettinati et al[31] showed such superiority—they used a double-blind, placebo-controlled study design to test the effectiveness of sertraline and naltrexone as monotherapy or their combination for the treatment of AUD in a group of 170 depressed patients. The study has demonstrated that the use of naltrexone alone was marginally different from placebo as well as the monotherapy with sertraline —both in terms of improvement in drinking outcomes and depressive symptoms—whereas the combination of 2 medications provided meaningful improvement both in drinking patterns and depressive symptomatology.[31] Of note, the latter was described as "approaching statistical significance" as though a meaningful effect was observed, it was not statistically significant. Despite obvious limitations of current research, the available data[19] indicate that there is a potential benefit in early initiation of antidepressant use in cases of major depressive episodes of questionable etiology and brings us to the question of treatment organization and sequencing.

Sequential vs parallel vs integrated treatment

Historically, concurrent disorders had been treated separately,[13] by separate providers, and often in a different timeline, for example, treatment of mood disorders would be commonly deferred until patient's addictions are treated first, in a sequential manner. This tendency was associated with the undertreatment of both disorders as many patients with addictions did not seek treatment or were not able to receive treatment for mood disorders due to ongoing addictive behaviors. Depressed patients whose treatment focused on depressive symptoms first would often have poor treatment responses unless their addictions were addressed at the same time. Recognizing the shortcomings of the sequential model, multiple treatment facilities started addressing both clinical problems in parallel fashion, that is, they would still be diagnosed and treated by separate providers or teams who would not always coordinate their efforts, which in turn resulted in subpar clinical responses. To improve the continuity of care and to provide patients with the most comprehensive and effective treatment, integrated care models started to emerge. While these models by definition require more resources to be invested in each patient's care, a significant boost in clinical effectiveness results in integrated care systems being more cost-effective than sequential or parallel treatments.[13]

Our secondary data analysis, that is, the glass-box testing of the integrated care pathway for concurrent depression and AUD[32] indicated that 71% of the overall treatment effect was attributable to the treatment integration, and the remaining 29%—to other resources (medications, psychoeducation, group and individual therapy, etc) spent on individual patients. Thus, we highly recommend adopting an integrated, holistic approach in the treatment of concurrent disorders, which should ideally be treated by an interdisciplinary team dynamically assessing patients' needs and providing them with a cohesive combination of psychopharmacological, psychotherapeutic, and psychosocial treatments.

Choice of antidepressants and antidipsotropic agents

There have been multiple clinical trials of various antidepressants and antidipsotropic agents for the treatment of concurrent AUD and MDD. The most recent meta-analysis of clinical trials[15] included the data from 13 clinical trials focused on depression scores in patients with substance use comorbidities and yielded a

small but statistically significant effect size of −0.16 (95% CI: −0.3 to −0.0.3, $P=0.02$). After exclusion of 4 studies of weak quality, authors concluded that selective serotonin reuptake inhibitors either alone or in combination with antidipsotropics had no significant effect on depressive symptomatology in patients with comorbid addictions. Non-SSRI antidepressants did not differ statistically from SSRIs. The meta-analysis of the drinking outcomes data pooled from 9 studies also yielded non-significant effects. At the same time, a review of individual studies showed that the combination of sertraline and naltrexone had a meaningful effect on drinking and depressive symptomatology,[31] as well as were imipramine[33] and fluoxetine.[34] It must be noted that tricyclic antidepressants, specifically imipramine, were proven to be effective for both depressive symptoms and abstinence from alcohol,[33] and that should serve as encouragement for their wider use in concurrent disorders practice. It must also be noted that tricyclic antidepressants are associated with a significantly higher risk of toxicity and lethal overdose and thus should be used with caution.[35] Alcohol consumption was predictably improved with the use of naltrexone or disulfiram.[36]

Despite the fact that only a few pharmacological agents were shown to produce a meaningful effect on depressive symptoms severity and alcohol use patterns and cravings, it must be noted that the research data are still limited to a small number of studies and further, more extensive research is needed. Based on the usage of multiple antidepressants and antidipsotropics in several hundred patients,[18,19] we did not observe any statistically significant benefit of the use of any specific pharmacological agent, and thus we would suggest considering the use of a broader spectrum of medications and implementing a more nuanced approach, that is, taking into consideration individual patients' characteristics such as other comorbidities, history of adverse effects and medical complications, as well as patient's preferences based on their beliefs and previous medication use history.

For example, the use of naltrexone would be contraindicated in patients receiving opioids for pain management, maintenance therapy for opioid use disorder, or an active recreational opioid use, but at the same time might be an excellent therapeutic choice for a patient with opioid use disorder is in early remission or for a patient with concurrent binge-eating disorder.[37] Similarly, disulfiram may be a better choice in a motivated and abstinence-oriented patient or in patient with comorbid cocaine use disorder,[38] but at the same time, it is not readily available in many locations in Canada and might pose a significant risk for patients prone to self-harm or impulsive drinking. Or, off-label use of pregabalin as an antidipsotropic agent[39] in a patient with a severe anxiety disorder may potentially reduce cravings, mitigate withdrawal symptoms, and alleviate anxiety.[40] Another medication commonly used off-label is topiramate, which has been shown to be effective in a series of clinical trials.[28,41] In addition to its antidipsotropic effects, it has shown to be effective with weight control, migraines, and mood stabilization in patients with bipolar, schizoaffective, and borderline personality disorders.[42,43] Most relevant to the treatment of MDD concurrent with AUD is that topiramate has been shown efficacy in augmenting the effects of SSRIs in the treatment of resistant MDD.[44] Unfortunately, this medication comes with a broad spectrum of side effects such as nephrolithiasis[45] and might come with significant cognitive side effects, which in turn would limit patients' ability to receive psychotherapy and decrease their quality of life.[46] For an excellent up-to-date review of the medications used for the treatment of AUD, their dosages, and side effects, please see Fairbanks et al (2020).[47]

Psychotherapy

As indicated earlier, psychotherapy should be an integral part of the treatment, not necessarily an alternative to, but complementary and synergistic with pharmacological treatments. Of note, there are multiple cases when psychotherapy may be the main treatment modality with minimal or no pharmacological interventions employed, based on a careful assessment of patients' needs, risk profile, and taking into consideration patient's preferences. For example, a patient who does not experience cravings for or withdrawal symptoms from alcohol may not require an antidipsotropic medication, or a patient whose depressive symptoms have significantly improved within the first weeks (or even days) of abstinence from alcohol may not require antidepressants. At the same time, our data indicate that these patients are a small minority and a combination of psychotherapy and pharmacological treatments is clinically indicated in the vast majority of cases.[19]

This recommendation is in line with the CANMAT Guidelines that recommend where feasible combined antidepressant and cognitive-behavioral therapy (CBT) or interpersonal therapy as first-line treatments for acute MDD and specifically indicate that the combination of antidepressants with psychotherapy is superior to either treatment alone.[48,49] Importantly, these recommendations do not necessarily take into account concurrent substance use disorders for which several psychotherapeutic treatments have been developed. Specifically, there is evidence supporting the use of motivational interviewing, contingency management, relapse prevention, and CBT in the treatment of substance use disorder, as well as the more flexible approach of combining various psychotherapeutic techniques under the umbrella of CBT and the use of pharmacological supports.[50–53] In

addition to that, there is an emerging concept of assimilative integration of motivational interviewing and brief behavioral activation therapy for depression, which appears to be an approach highly relevant to the concurrent disorders practice.[54]

In special cases, when evidence-based structured psychotherapy cannot be provided or arranged for, we would still recommend using several highly resource-effective approaches such as brief interventions,[55] bibliotherapy,[56] and internet-based therapies[57] as there is growing evidence supporting them.

Ultimately, given the versatility of CBT and its demonstrated universal effectiveness for treatment of both addictions and mood disorders, we would recommend the use of a CBT-based approach tailored to the treatment of concurrent disorders, combined with pharmacotherapy when indicated, in a group or individual format based on the settings and resources available.[17]

What to expect?

When starting the treatment, risks and benefits are assessed and the expectations of both patients and treatment team need to be managed as both over- and underestimation of potential benefits of treatment may negatively impact the clinical outcomes.[58] Historically, the outcomes of concurrent disorders treatment programs are underwhelmingly poor, especially, when sequential or parallel treatment models are used—patients demonstrate poor medication compliance, high attrition rates, low engagement in therapy, and ultimately low rates of remission, minimal or no changes in drinking patterns and depressive symptomatology.[16,18]

Special attention must be paid to the emergence of suicidal ideation, especially in the first weeks of treatment with antidepressants,[59] as well as due to relapses and associated disinhibition, impulsivity, and impaired judgment.[60] Routine screening for suicidal ideation should be an integral part of the treatment program, as well the monitoring of the treatment indicators associated with it such as worsening of depressive symptomatology and drinking patterns, sense of hopelessness, and adverse psychosocial events. Emergency intervention plans and psychoeducation about suicidality and crisis resources are paramount. We believe that such approaches should and naturally are incorporated into integrated treatment models by their very design and monitoring systematically occurs on a regular and usually frequent basis.

Moreover, our data indicate that when an integrated care model is used that incorporates both psychotherapy and pharmacotherapy tailored to individual patients' needs and delivered in a coordinated fashion,[17] the clinical outcomes significantly improve—in a large sample of patients with concurrent MDD and AUD we have observed 81.5% retention rate vs 30.9% in a cohort of historical controls. At 16-week follow-up, the survival (non-dropout) probability was 81.4% (95%CI: 73.4–90.4%) and 27.2% (95%CI: 19.0–13.8%) in integrated care and treatment as usual cohorts, respectively ($P < 0.001$).[18]

By the end of the 16-week standardized treatment protocol, 69.1% of patients were drinking within Canada's Low-Risk Drinking guidelines (vs 42.0% in the treatment as a usual cohort) with effect sizes ranging between 0.9 and 1.1 vs 0.3 and 0.5, respectively.[18] The cravings' intensity in integrated treatment cohort as measured by Penn Alcohol Craving Scale[61] decreased by 42% from 17.6 to 12.0 (ES = 0.6, $P < 0.001$) and depression symptoms' severity as measured by Quick Inventory of Depressive Symptomatology[62] decreased by 31%, from 14.6 to 10.0 (ES = 0.8, $P < 0.001$). These data illustrate the typical outcomes of treatment as usual and integrated treatment approaches and can be used to set the expectations for the treatment team as well as for psychoeducation.

Measurement-based care

The routine use of quantitative clinical tools facilitates screening and early identification of concurrent disorders allows for establishing the baseline parameters and for setting the treatment goals in a measurable and easy-to-understand format as well as for monitoring patients' progress and adjustment of the therapeutic approach.[17,63] CANMAT guidelines support this recommendation in the context of pharmacological treatment of mood disorders.[63]

Based on our clinical data,[17,19,32] the use of a selection of brief and self-administered questionnaires is an integral and cost-effective part of the treatment process for several reasons: first, routine use of screening tools allows for early identification of concurrent disorders, especially mild forms—as patients might not disclose and clinicians might not routinely screen for them; Second, the mere fact of measurement tends to improve the outcomes, the phenomenon well-known in the research literature as the Hawthorne effect;[64] third, availability of quantifiable data improves communication between care providers; forth, the use of clinical scales may help with the understanding of the effectiveness of specific treatments, for example, acamprosate, an anti-craving medication, often does not eliminate cravings completely, which makes it difficult to observe its effects, but with the use of a validated craving scale its effects become evident. Or, alternatively, the absence of meaningful change on a clinical rating scale may prompt medication switch. Finally, the use of clinical measures allows for the development of structured clinical algorithms such as, for example, the Texas Medication Algorithms developed for a variety of mental illnesses.[65]

A set of clinical tools that could be used to screen and monitor patients' presentation might include the following instruments: 1) AUD Identification Test (AUDIT) or its concise versions (AUDIT-C and AUDIT-3),[66] which allow for both screening for and quantification of the severity of alcohol-related problems; 2) Patient Health Questionnaire[67] or Quick Inventory of Depressive Symptomatology[62] for monitoring of depressive symptoms; 3) Penn Alcohol Craving Scale[61] for assessment of cravings severity; and 4) alcohol consumption patterns operationalized by number of standard drinks consumed per week, per drinking day, number of drinking days, and number of heavy drinking days per week.[32]

We would like to illustrate the effect of the transition to measurement-based care on clinical outcomes with the study of Guo et al[68] who conducted a randomized clinical trial of treatment of MDD with a standard set of clinical tools. They randomized study participants into 2 groups —measurement-based care group (n = 61) and a standard treatment group (n = 59). The measurement-based care group, which used guideline- and rating scale-based decision-making process, demonstrated significantly better outcomes: higher response rate (86.9% vs 62.7%), higher remission rate (73.8% vs 28.8%), much shorter time to response (5.6 vs 11.6 weeks for response, 10.2 vs 19.2 weeks for remission), and larger reduction in Hamilton Depression Rating Scale[69] (−17.8 vs 13.6). The measurement-based care approach in their study also contributed to a much higher number of treatment adjustments (44 vs 23) and higher final medication dosages, which emphasizes the role of routine use of clinical rating scales in the clinical decision-making process and solidifies our recommendation to use them routinely and widely to monitor all key aspects of clinical presentation in concurrent AUD and MDD, that is, depressive symptomatology, drinking patterns, cravings, side effects, and quality of life.[1,19,70]

CONCLUSIONS

Based on the review of the available research evidence and the clinical data from a large multi-site clinical project we recommend 1) collecting extensive history of concurrent disorders and establishing the temporal relationship between AUD and MDD; 2) in cases when the etiology of depressive episode is unclear early use of antidepressants may be beneficial; 3) naltrexone, disulfiram, sertraline, fluoxetine, and imipramine have the best evidence supporting their use for treatment of concurrent MDD and AUD, but a wider selection of pharmacological agents and more nuanced approach is encouraged; 4) concomitant use of antidepressants, antidipsotropics, and various forms of psychotherapy in 1 integrated setting is advised; 5) the response rates, even in the best-case scenarios might be underwhelmingly low, but integrated care models are shown to be superior to sequential or parallel care approaches, 6) the use of measurement-based care is strongly advised for better outcomes, and 7) the clinical outcomes presented in the article can be used for psychoeducation and as a benchmark for clinical teams.

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