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BIBIANA BOLTEN LUCION LORETO

DESENVOLVIMENTO DE UM MODELO INTEGRATIVO, DINÂMICO E TRANSDIAGNÓSTICO PARA ADIÇÕES

Porto Alegre
2026

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Tese apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de doutor em Psiquiatria e Ciências do Comportamento.

Orientador: Prof. Dr. Félix Henrique Paim Kessler

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Para meus avôs, Angelo e Noé, que não conheci, mas cujas histórias na Medicina e na Psiquiatria sempre me inspiraram.

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Ações? O que eu vi, sempre, é que
toda ação principia mesmo é por uma palavra
pensada. Palavra pegante, dada ou guardada,
que vai rompendo rumo.

Guimarães Rosa

Grande Sertão: Veredas

RESUMO

Os transtornos aditivos são psicopatologias de alta prevalência e carga de doença, mas ainda carecem de modelos diagnósticos e terapêuticos capazes de integrar a complexidade dos fatores envolvidos. Muitas teorias já foram propostas para explicar os mecanismos que levam ao desenvolvimento da adição. Embora a neurociência tenha avançado substancialmente nas últimas décadas, muitos desses achados ainda possuem impacto restrito na prática clínica, configurando uma importante lacuna translacional. Nesse contexto, torna-se necessária a construção de modelos mais integrativos, dinâmicos e transdiagnósticos, capazes de aproximar neurobiologia, comportamento, emoções, contexto ambiental e tomada de decisão terapêutica personalizada.

Esta tese propõe um modelo baseado em um novo conceito, a "mente predostática", que combina os princípios de predição e homeostase para compreender os mecanismos que sustentam as adições. Para isso foi utilizada uma abordagem metodológica baseada em revisões narrativas da literatura científica conduzidas de forma sistematizada, abrangendo teorias etiológicas das adições, modelos diagnósticos tradicionais e alternativos, além das principais intervenções farmacológicas e psicossociais com evidência empírica. Essa revisão permitiu a integração de conceitos para o desenvolvimento dos modelos e a proposição de ferramentas clínicas adaptadas ao modelo da mente predostática.

O resultado desta tese é composto por três artigos. O primeiro artigo, "*Advanced Cognitive Emotional Regulation Therapy (ACERT) for Addiction Treatment*", traz uma proposta inicial de um modelo de avaliação, medidas e tratamento das adições. propôs um modelo inicial de avaliação e tratamento centrado na regulação cognitivo-emocional, organizando sintomas em dimensões clínicas relacionadas à desregulação emocional, impulsividade, compulsão e sofrimento psíquico. O modelo sugeriu que o comportamento aditivo pode representar uma tentativa de autorregulação diante de estados internos disfuncionais, integrando intervenções psicoterápicas e psicofarmacológicas em uma lógica dimensional e personalizada.

O segundo artigo, "*Proposing an integrative, dynamic and transdiagnostic model for addictions: dysregulation phenomena of the three main modes of the predostatic mind*", desenvolveu de forma mais abrangente o modelo da mente predostática e introduziu o conceito DREXI3 (Dysregulation Phenomena of the Three Main Modes of the Predostatic Mind). Nesse modelo, as adições são compreendidas como padrões crônicos de desregulação envolvendo três modos principais da mente — Seek Mode, Alarm Mode e Balance Mode — relacionados

respectivamente à busca de recompensa, resposta à ameaça e restauração do equilíbrio homeostático. O artigo também propôs que emoções, pensamentos e comportamentos possam ser entendidos como respostas preditivas voltadas à busca de equilíbrio interno diante de estímulos ambientais e estados de sofrimento.

Por fim, o terceiro artigo, "*BE-CERTIF(AI)D in Addiction Treatment: Personalized Regulation Therapy with Integrated, Dynamic and Transdiagnostic Strategies using Artificial Intelligence*", ampliou essa perspectiva ao propor um modelo terapêutico transdiagnóstico e personalizado baseado em dimensões sintomáticas, predição de risco, regulação homeostática e integração de estratégias farmacológicas, psicossociais e ferramentas de inteligência artificial. O modelo incorporou a ideia de intervenções orientadas por perfis individuais de desregulação emocional, cognitiva e comportamental, alinhando-se aos princípios emergentes da psiquiatria de precisão.

Palavras-chave: adições, modelo de avaliação, modelo de tratamento, transdiagnóstico, predição de risco, homeostase, regulação.

ABSTRACT

Addictive disorders are highly prevalent psychopathologies with a significant disease burden, yet diagnostic and therapeutic models capable of integrating the complexity of the factors involved are still lacking. Many theories have been proposed to explain the mechanisms that lead to the development of addiction. Although neuroscience has advanced substantially in recent decades, many of these findings still have a limited impact on clinical practice, representing a significant translational gap. In this context, it becomes necessary to construct more integrative, dynamic, and transdiagnostic models capable of bridging neurobiology, behavior, emotions, environmental context, and personalized therapeutic decision-making.

This thesis proposes a model based on a new concept, the "Predostatic Mind," which combines the principles of prediction and homeostasis to understand the mechanisms that underpin addictions. To this end, a methodological approach was used based on systematic narrative reviews of the scientific literature, encompassing etiological theories of addictions, traditional and alternative diagnostic models, as well as the main pharmacological and psychosocial interventions with empirical evidence. This review allowed for the integration of concepts for the development of the models and the proposition of clinical tools adapted to the Predostatic Mind model.

The result of this thesis consists of three articles. The first article, “Advanced Cognitive Emotional Regulation Therapy (ACERT) for Addiction Treatment,” presents an initial proposal for a model of assessment, measurement, and treatment of addictions. It proposed an initial assessment and treatment model centered on cognitive-emotional regulation, organizing symptoms into clinical dimensions related to emotional dysregulation, impulsivity, compulsion, and psychological distress. The model suggested that addictive behavior may represent an attempt at self-regulation in the face of dysfunctional internal states, integrating psychotherapeutic and psychopharmacological interventions within a dimensional and personalized framework.

The second article, “Proposing an integrative, dynamic, and transdiagnostic model for addictions: dysregulation phenomena of the three main modes of the predostatic mind,” developed the Predostatic Mind model more comprehensively and introduced the concept of DREXI3 (Dysregulation Phenomena of the Three Main Modes of the Predostatic Mind). In this model, addictions are understood as chronic patterns of dysregulation involving three main modes of the mind—Seek Mode, Alarm Mode, and Balance Mode—related respectively to reward seeking, threat response, and restoration of homeostatic balance. The article also

proposed that emotions, thoughts, and behaviors can be understood as predictive responses aimed at seeking internal balance in the face of environmental stimuli and states of suffering.

Finally, the third article, “BE-CERTIF(AI)D in Addictions: Personalized Regulation Therapy with Integrated, Dynamic, and Transdiagnostic Strategies using Artificial Intelligence,” expanded this perspective by proposing a transdiagnostic and personalized therapeutic model based on symptomatic dimensions, risk prediction, homeostatic regulation, and the integration of pharmacological, psychosocial strategies and artificial intelligence tools. The model incorporated the idea of interventions guided by individual profiles of emotional, cognitive, and behavioral dysregulation, aligning with the emerging principles of precision psychiatry.

Keywords: addictions, evaluation model, treatment model, transdiagnosis, risk prediction, homeostasis, regulation.

LISTA DE ILUSTRAÇÕES

Figura 1 - Modelo de circuitos interativos nos quais as disrupções contribuem para comportamentos do tipo compulsivo subjacentes à adição 21

LISTA DE ABREVIATURAS E SIGLAS

DSM-5-TR	Manual Diagnóstico e Estatístico de Transtornos Mentais, 5ª Edição, Texto Revisado
HIV	Human Immunodeficiency Virus
TDAH	Transtorno de déficit de atenção e hiperatividade
ASI	Addiction Severity Index
LENAD	Levantamento Nacional de Álcool e Drogas
DALY	Disability-adjusted Life Years
ICD-11	Classificação Internacional de Doenças, 11ª Revisão
RDoC	Research Domain Criteria
HiTOP	Hierarchical Taxonomy of Psychopathology
DREXI3	Dysregulation of the three main modes of the predostatic mind
ACERT	Advanced Cognitive Emotional Regulation Therapy
BE-CERTIF(AI)D	Personalized Regulation Therapy with Integrated, Dynamic and Transdiagnostic Strategies using Artificial Intelligence

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1 APRESENTAÇÃO

Esta tese nasceu da prática clínica, do contato diário com pacientes que sofrem com transtornos aditivos e da inquietação progressiva diante da complexidade humana que frequentemente ultrapassa as classificações diagnósticas tradicionais. Ao longo da formação em Psiquiatria — especialmente durante o quarto ano de residência com ênfase em Adições no Hospital de Clínicas de Porto Alegre — tornou-se cada vez mais evidente que muitos pacientes compartilhavam sofrimento intenso, recaídas recorrentes, impulsividade, dificuldades emocionais e tentativas constantes de buscar algum tipo de equilíbrio interno, ainda que por caminhos frequentemente autodestrutivos.

Ao mesmo tempo, também surgiam angústias clínicas importantes. Apesar dos avanços expressivos da neurociência nas últimas décadas e da disponibilidade crescente de intervenções psicoterápicas e psicofarmacológicas, muitos pacientes continuavam apresentando sofrimento persistente, desregulação emocional, dificuldades relacionais e respostas terapêuticas apenas parciais. Frequentemente, havia a sensação de que os modelos disponíveis ainda eram insuficientes para compreender plenamente a complexidade emocional, biológica e comportamental envolvida nas adições.

Na prática cotidiana, tornava-se difícil enxergar as adições apenas como alterações isoladas do sistema de recompensa ou como categorias diagnósticas rígidas. Muitos pacientes pareciam utilizar substâncias, comportamentos compulsivos ou padrões repetitivos não apenas pela busca de prazer, mas também como tentativas de aliviar sofrimento, reduzir estados internos aversivos, silenciar angústias ou recuperar temporariamente uma sensação de estabilidade emocional. Essas observações aproximavam conceitos relacionados ao estresse, à regulação emocional, à impulsividade, ao comportamento, à farmacologia, à psicoterapia e aos mecanismos neurobiológicos de adaptação humana.

Foi nesse contexto que surgiu a aproximação com o modelo da “mente predostática”, proposto pelo orientador desta tese, Prof. Felix Kessler. A identificação com essa perspectiva ocorreu justamente pela tentativa de integrar diferentes dimensões do sofrimento psíquico dentro de uma lógica mais dinâmica, funcional e humana, aproximando neurobiologia, emoções, comportamento, estresse e busca de equilíbrio interno. Mais do que um modelo puramente teórico, essa proposta parecia dialogar diretamente com aquilo que era observado diariamente nos pacientes atendidos no campo das adições.

A construção desta tese representa, portanto, um percurso compartilhado entre orientador e orientanda marcado por inquietações científicas, observações clínicas e pelo desejo de contribuir para uma compreensão mais integrativa das adições. As ideias apresentadas aqui foram sendo desenvolvidas progressivamente a partir da integração entre experiência clínica, literatura científica, discussões acadêmicas e reflexões sobre os limites e possibilidades da Psiquiatria contemporânea.

Mais do que oferecer respostas definitivas, este trabalho busca abrir novas possibilidades de reflexão sobre pacientes que frequentemente sofrem de forma silenciosa, carregam intenso estigma e vêm aumentando progressivamente em prevalência nas últimas décadas. Em um cenário no qual as adições se tornam cada vez mais multifacetadas e desafiadoras, talvez compreender melhor os mecanismos relacionados à regulação emocional, ao estresse, à busca de recompensa e às tentativas humanas de adaptação possa representar um pequeno passo em direção a abordagens terapêuticas mais precisas, individualizadas e, sobretudo, mais humanas.

2 INTRODUÇÃO

Este capítulo descreve o referencial teórico utilizado para escrever esta tese e os artigos que a compõem. São apresentados conceitos da psiquiatria de adição, da epidemiologia e da metodologia de construção de teorias. Na seção 1.1, são apresentados conceitos sobre os transtornos aditivos; na seção 1.2, são descritos dados sobre a epidemiologia dos transtornos aditivos; na seção 1.3, são descritos os principais modelos diagnósticos existentes no campo das adições; na seção 1.4, são descritas as limitações existentes nos modelos atuais de avaliação e tratamento; na seção 1.5, são apresentados conceitos da metodologia de construção de teorias e o racional para a proposta de um novo modelo de avaliação e tratamento.

2.1 OS TRANSTORNOS ADITIVOS

Os transtornos aditivos englobam tanto aqueles relacionados ao uso de substâncias psicoativas quanto as chamadas adições comportamentais. Embora estas últimas tenham ganhado progressivamente mais atenção nos últimos anos, sua classificação diagnóstica no Manual Diagnóstico e Estatístico de Transtornos Mentais, 5ª Edição, Texto Revisado (DSM-5-TR) se restringe ao transtorno do jogo (1). Em relação aos transtornos por uso de substâncias, o DSM-5-TR descreve essa condição como um conjunto de sintomas cognitivos, emocionais e fisiológicos. Embora haja critérios diagnósticos padronizados, pode haver variações entre os sintomas conforme a substância envolvida.

Para fins de organização geral, os sintomas podem ser agrupados em categorias como “baixo controle”, “deterioração social”, “uso arriscado” e “critérios farmacológicos”. Os sintomas relacionados ao baixo controle incluem: o consumo da substância em quantidades maiores ou por um período de tempo mais longo do que o pretendido; o desejo persistente de reduzir ou cessar o uso da substância, que pode ser acompanhado de esforços mal-sucedidos; o relato de muito tempo despendido na obtenção da substância, no uso e na recuperação de seus efeitos; e a ocorrência de fissura, manifestada por uma necessidade intensa de consumir a substância. Os sintomas de prejuízo social são relacionados ao fracasso no cumprimento de obrigações; à persistência do uso da substância apesar de problemas sociais ou interpessoais; e à redução de atividades sociais ou profissionais importantes em função do uso da substância. O uso arriscado se refere ao consumo em situações que oferecem risco à integridade física e à

persistência de problemas físicos ou psicológicos relacionados à substância. Por fim, os critérios farmacológicos tratam dos conceitos de tolerância e abstinência. A tolerância ocorre quando é necessária uma dose maior da substância para se obter o efeito desejado ou quando o efeito é reduzido com o uso habitual. Já a abstinência é o conjunto de sintomas que se manifestam quando a concentração da substância diminui após um período de uso prolongado. De modo geral, as adições tendem a apresentar curso crônico, que pode ser marcado por períodos de remissão e recaída (1).

Embora haja muitas semelhanças entre os diferentes transtornos aditivos, as manifestações também podem ser muito heterogêneas (2). Parte dessa heterogeneidade se deve ao fato de que as adições são frequentemente acompanhadas por outros transtornos psiquiátricos. Entre as comorbidades mais comuns estão os transtornos de humor, os transtornos de ansiedade (3), os transtornos de personalidade (4) e o transtorno de déficit de atenção e hiperatividade (TDAH) (5). Comorbidades clínicas também são mais comuns nesse grupo populacional, havendo como exemplos a tuberculose e o HIV (6,7). Consequentemente, indivíduos que usam substâncias parecem utilizar os serviços de saúde com maior frequência do que a população geral (8). De forma similar, a presença de comorbidades clínicas já foi associada a readmissões a internações psiquiátricas após uma alta recente (9). Em resumo, comorbidades clínicas e psiquiátricas podem influenciar de diferentes formas o prognóstico de pacientes com transtornos aditivos.

A gravidade e a sintomatologia dos transtornos aditivos também podem ser influenciadas por fatores psicossociais (10,11). Aspectos socioeconômicos afetam a prevalência de transtornos psiquiátricos em geral e também podem aumentar o risco de determinados desfechos relacionados a substâncias psicoativas (12,13). Fatores como eventos estressores, facilidade de acesso a substâncias e comportamento dos pares têm um papel tanto no desenvolvimento quanto na manutenção dos transtornos por uso de substâncias (14). A recaída, que se refere ao retorno a um padrão anterior de uso de substância, consiste em um dos maiores desafios no tratamento dessas condições, e está diretamente relacionada a fatores ambientais (15–17).

Considerando a origem multifatorial e a heterogeneidade das manifestações clínicas das adições, a avaliação da sintomatologia pode se tornar bastante complexa. Um dos principais instrumentos utilizados no campo das adições é o Addiction Severity Index (ASI), que atualmente está em sua sexta versão. Esse instrumento consiste em uma entrevista estruturada, capaz de avaliar seis áreas potencialmente afetadas pelo transtorno (18). O ASI-6 foi validado para uso no Brasil e é frequentemente utilizado para fins de avaliação clínica e em protocolos

de pesquisa (19). Porém, cabe ressaltar que o desenvolvimento de novos instrumentos poderia proporcionar uma avaliação mais detalhada desse perfil de pacientes e trazer benefícios para a prática clínica.

2.2 A EPIDEMIOLOGIA DOS TRANSTORNOS ADITIVOS

Há uma tendência mundial de que os transtornos aditivos sigam sendo condições de alta prevalência. O World Drug Report publicado pelas Nações Unidas em 2021 revela que, entre os anos de 2010 e 2020, houve um aumento no número de pessoas que relataram uso de substâncias psicoativas nos últimos 12 meses (20). A publicação da edição mais recente do Levantamento Nacional de Álcool e Drogas (LENAD III) trouxe dados atualizados sobre a epidemiologia das adições na população brasileira, sendo alguns deles alarmantes. Em relação ao álcool, que se trata de uma das substâncias de uso mais prevalente, até 14,2% da população em geral consumiu álcool em binge no último ano, ou seja, consumiu 4 ou 5 doses em um período de 2 horas. Adicionalmente, mais de um terço da população apresentou consumo pesado episódico de álcool no último ano (21).

Os transtornos psiquiátricos e os transtornos aditivos estão associados a uma alta carga de doença. Em 2016, esse grupo de transtornos era responsável por 7% da carga global de doença medida em anos de vida perdidos ajustados por incapacidade (Disability-Adjusted Life Years, DALY) (22). Entre 1990 e 2019, houve um aumento na taxa de DALY por uso de substâncias na população com idade entre 10 e 24 anos (23). Diferentemente de outros transtornos psiquiátricos, as adições foram associadas a uma maior carga de doença principalmente em homens (22).

Os transtornos aditivos também são acompanhados por uma significativa mortalidade associada. Entre os anos de 2007 e 2017, o número de mortes relacionadas a transtornos por uso de substâncias aumentou de 284000 para 352000. O transtorno por uso de álcool responde pela maior parte das mortes relacionadas a substâncias psicoativas, seguido pelo transtorno por uso de opioides (24). Os dados epidemiológicos descritos evidenciam o impacto que os transtornos aditivos têm na saúde e na qualidade de vida dos pacientes acometidos e a consequente necessidade de aprimorar os tratamentos disponíveis.

2.3 OS MODELOS DIAGNÓSTICOS NOS TRANSTORNOS ADITIVOS

Diferentes modelos teóricos foram propostos ao longo dos anos no intuito de explicar o desenvolvimento e a manutenção das adições. As teorias biológicas têm sido bastante estudadas nos últimos anos e apresentam como vantagem a maior possibilidade de serem testadas por meio de exames de neuroimagem ou marcadores biológicos, por exemplo (25). Estudos de Volkow et al. Foram fundamentais para o desenvolvimento do modelo biológico da adição, que destaca o papel da dopamina e do sistema de recompensa na manutenção do transtorno (26).

O modelo biológico define a adição como uma "doença do cérebro", pois estudos de neuroimagem revelaram como diferentes circuitos cerebrais são ativados em momentos como a intoxicação e a abstinência (27). Koob & Volkow desenvolveram um modelo baseado na neuropsicofarmacologia e na neuroimagem da adição. Destaca-se nesse modelo a proposta de que a adição pode ser compreendida em três estágios, sendo cada um associado a um circuito neurobiológico e a características clínicas específicas. O estágio de *binge* e intoxicação está associado ao aumento da liberação de dopamina. Inicialmente, a liberação deste neurotransmissor está diretamente associada à ativação de circuitos de recompensa pela substância. Com a progressão do uso, a liberação de dopamina passa a ocorrer como uma resposta antecipatória a estímulos que foram condicionados ao uso da substância. O segundo estágio, de abstinência e afeto negativo, evidencia a redução da motivação para reforçadores naturais diante da liberação mais potente de dopamina associada às substâncias psicoativas. Adicionalmente, a liberação de dopamina tende a diminuir com o desenvolvimento da adição e o indivíduo fica mais propenso à reatividade ao estresse e ao surgimento de emoções negativas. Por fim, o estágio de preocupação e antecipação se refere às repercussões que as mudanças nos circuitos de recompensa têm na região do córtex pré-frontal, afetando funções executivas (28,29). Os circuitos relacionados aos estágios descritos estão representados na Figura 1.

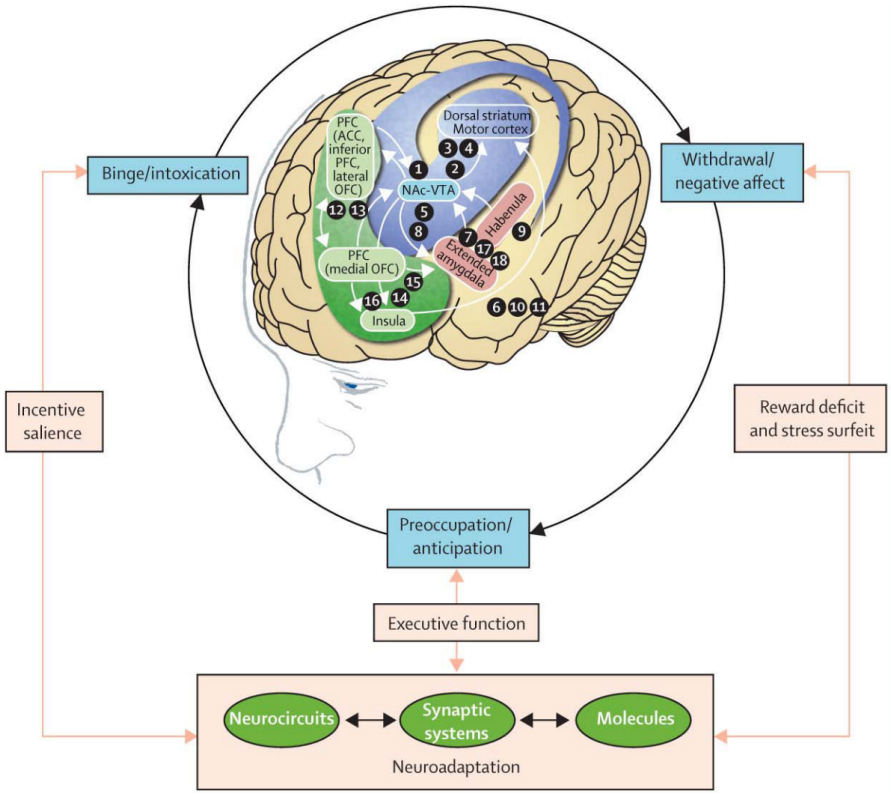


Figura 1 - Modelo de circuitos interativos nos quais as disrupções contribuem para comportamentos do tipo compulsivo subjacentes à adição

Fonte: Adaptado de Koob e Volkow (2016). (29)

O modelo da adição como uma doença do cérebro trouxe inegáveis benefícios, pois o maior conhecimento dos substratos neurobiológicos dos transtornos aditivos favorece o desenvolvimento de terapêuticas mais direcionadas. Adicionalmente, o entendimento de que um transtorno possui uma base orgânica favorece a redução do estigma. No entanto, o modelo também já foi alvo de controvérsias e questionamentos quanto ao seu impacto na prática clínica e nas políticas públicas. Críticos desse modelo alegam que as evidências em modelos animais e em neuroimagem são escassas, que os tratamentos na área de adições não se tornaram mais efetivos e que a repercussão em políticas públicas foi modesta (30,31).

Como um contraponto ao modelo biológico, a teoria da automedicação já foi bastante explorada na literatura. Ela postula que a predisposição ao comportamento aditivo está relacionada à ocorrência de afetos negativos e à presença de comorbidades psiquiátricas. Mesmo indivíduos que fazem uso de múltiplas substâncias costumam ter uma substância de escolha, e esta seria um meio para regular emoções negativas. Essa teoria foi baseada inicialmente na observação de usuários de opioides e cocaína. Foi sugerido que os opioides

seriam utilizados como uma tentativa de controlar impulsos agressivos. Já a cocaína seria consumida com o objetivo de regular sintomas de humor, como sintomas depressivos (32).

A hipótese da automedicação foi reavaliada ao longo dos anos, sendo possível encontrar evidências favoráveis e contrárias a essa proposta. Em estudos posteriores, Khantzian propôs outras correlações entre substâncias e sintomas, como entre a nicotina nos sintomas depressivos e o álcool no transtorno de estresse pós-traumático (33) Apesar dos questionamentos na literatura, a hipótese da automedicação é considerada um paradigma importante na avaliação dos transtornos aditivos ao considerar a relevância de afetos negativos e de vulnerabilidades do indivíduo (34).

A hipótese da automedicação pode ser compreendida como o principal modelo no âmbito das teorias homeostáticas das adições — aquelas que consideram o transtorno aditivo como uma busca por regulação em resposta a afetos negativos e contingências ambientais (35). A homeostase é definida como a manutenção de estabilidade de um organismo que se adapta a mudanças externas. Trata-se de um processo dinâmico, que envolve diversos sistemas. Uma descontinuidade nos processos homeostáticos poderia levar à patologias (36). Nesse contexto, o uso de substâncias surgiria como uma tentativa de retornar ao equilíbrio durante a manifestação de afetos negativos. Entretanto, a repetição de um comportamento disfuncional, como o uso de substâncias, terminaria por manter o ciclo da desregulação (37). Uma teoria que integrasse tanto aspectos biológicos quanto homeostáticos poderia ajudar a direcionar tratamentos que contemplassem essas diferentes dimensões do indivíduo.

2.4 AS LIMITAÇÕES DOS MODELOS DIAGNÓSTICOS NA AVALIAÇÃO E NO TRATAMENTO DOS TRANSTORNOS ADITIVOS

Embora diversos estudos tenham se dedicado à compreensão dos transtornos aditivos, a avaliação e o tratamento dessas condições continuam um desafio. O diagnóstico das adições ainda se baseia em sistemas categóricos, como o DSM-5-TR (1) e a ICD-11 (38), que podem se mostrar insuficientes na compreensão de casos complexos. Classificações dimensionais, como o Research Domain Criteria (RdoC) (39) e o Hierarchical Taxonomy of Psychopathology (HiTOP) (40) surgiram como uma alternativa, mas permanece a necessidade de um modelo diagnóstico que integre perspectivas distintas.

Os métodos de avaliação e quantificação dos sintomas também se mostram essenciais para o manejo adequado dos transtornos aditivos. O ASI-6 possibilita uma avaliação ampla de

sintomas relacionados à adição (41), mas, de modo geral, escalas ainda são pouco utilizadas na prática clínica. Novos instrumentos de avaliação e quantificação deveriam considerar a relação dos sintomas com a desregulação emocional e comportamental.

Alguns autores afirmam que há uma crise translacional em curso nesta área, pois os extensos avanços na pesquisa biológica não encontram repercussão significativa na prática clínica (42,43). A literatura científica apresenta evidências bem embasadas de tratamento farmacológico para determinadas substâncias psicoativas. A naltrexona, o acamprosato (44) e o dissulfiram são os tratamentos farmacológicos de escolha para o transtorno por uso de álcool (45). O tabagismo também dispõe de alternativas farmacológicas para tratamento, como a vareniclina — que é a medicação mais eficaz —, a bupropiona (46) e a terapia de reposição de nicotina (47). Em relação ao transtorno por uso de opioides, o tratamento pode incluir tanto os antagonistas de opioides quanto os agonistas parciais e agonistas/antagonistas (48,49).

Para outras substâncias psicoativas, as evidências disponíveis para tratamento farmacológico são menos consistentes, restando como alternativa as abordagens psicossociais. Embora sejam amplamente utilizadas na prática clínica, essas técnicas tendem a apresentar um nível de evidência menos sólido do que os tratamentos citados anteriormente. A entrevista motivacional apresenta efeitos positivos em alguns estudos, sendo comumente aplicada como uma estratégia inicial do tratamento (50). A terapia cognitivo-comportamental é uma linha de psicoterapia com bastante embasamento para os transtornos por uso de substâncias (51–53), com destaque para as técnicas de prevenção de recaída (54). O manejo de contingências (55,56), a psicoterapia de grupo (57) e os programas de 12 passos para o transtorno por uso de álcool também estão entre as intervenções que se mostraram efetivas (58).

Diante do fato de que os tratamento já estabelecidos parecem abordar de maneira parcial os mecanismos da adição, surge como alternativa a compreensão dos transtornos aditivos como um processo multidimensional, envolvendo sistemas como regulação emocional, controle cognitivo, formação de hábitos e responsividade ao estresse (14,29). Disfunções nesses sistemas poderiam favorecer o uso de substâncias e a manutenção desse comportamento ao longo do tempo.

A desregulação emocional é um aspecto central no desenvolvimento e na manutenção dos comportamentos aditivos. Indivíduos com transtornos por uso de substâncias costumam apresentar dificuldades em identificar, tolerar e regular emoções negativas. Conforme a hipótese da automedicação, as substâncias psicoativas seriam utilizadas como uma tentativa de alívio do estresse (59,60). Todavia, muitos modelos de tratamento ainda abordam a desregulação emocional apenas de forma indireta.

Alterações no controle cognitivo e na capacidade de tomar decisões também são características da adição. Estudos de neuroimagem já demonstraram que indivíduos com transtornos por uso de substâncias apresentam alterações funcionais no córtex pré-frontal — região responsável pelo controle executivo e pela inibição de impulsos (61). Apesar dos avanços da neuroimagem, esses processos cognitivos ainda são pouco abordados em termos de tratamento.

A formação de hábito se refere a mecanismos de aprendizado comportamental. O uso repetido de uma substância reforça esse comportamento e termina por transformá-lo em um hábito de padrão compulsivo. Esse processo é mediado por modificações no sistema de recompensa dopaminérgico e no estriado (62). Algumas intervenções terapêuticas, como o manejo de contingências (55,56), tem um enfoque comportamental, mas podem se mostrar insuficientes.

A presença de estresse crônico já foi associada ao desenvolvimento do uso de substâncias e também ao risco de recaída. Já foi constatado que indivíduos com uso de substâncias apresentam desregulação do eixo hipotálamo-hipófise-adrenal (14,63). No entanto, a resposta ao estresse ainda é um aspecto pouco abordado no tratamento das adições.

Os modelos de tratamento nas adições tendem a ser direcionados a um componente específico do processo, o que pode levar a falhas terapêuticas. Adicionalmente, os pacientes com transtornos aditivos são um grupo bastante heterogêneo em termos de genética, personalidade, condições clínicas e contexto socioeconômico (21,64). Esses dados sugerem que adotar o mesmo protocolo de tratamento pode ser adequado para pacientes com características diferentes. A psiquiatria de precisão reforça essa proposta de que as intervenções devem se tornar mais personalizadas (65). No contexto das adições, isso envolve fazer uma melhor avaliação da regulação emocional, do controle cognitivo, dos padrões de aprendizado comportamental, da responsividade ao estresse e do contexto social do indivíduo. Essas limitações sinalizam a necessidade de novos modelos, capazes de integrar diferentes níveis de avaliação. Uma avaliação que integre influências biológicas, psicológicas e comportamentais possibilitaria o desenvolvimento de tratamentos mais personalizados

2.5 A CONSTRUÇÃO DE TEORIAS

Apesar dos avanços científicos das últimas décadas, ainda há desafios no processo de avaliação e tratamento dos transtornos mentais. Fried sugere que há uma tendência a reduzir

o estudo dessas patologias ao diagnóstico e a elementos individuais do transtorno, em detrimento de uma compreensão mais ampla (66). Nesse contexto, a construção de novas teorias se torna fundamental para expandir a compreensão desses fenômenos.

A construção de teorias é um processo essencial para o desenvolvimento da ciência. No campo da saúde mental, a metodologia de pesquisa é centrada principalmente na capacidade de se testar hipóteses empíricas, como é feito nos ensaios clínicos. Contudo, há poucos estudos na área focados na construção de teorias. Diante dessas lacunas, Borsboom et al. Desenvolveram uma metodologia de construção de teoria constituída de cinco etapas. Inicialmente, deve ser identificado um domínio de fenômenos empíricos a ser explicado. A seguir, vem a construção de uma prototeoria para explicar esses fenômenos. Na terceira etapa, essa prototeoria é utilizada para a construção de um modelo formal. Posteriormente, é analisada a adequação explicativa do modelo. Por fim, é avaliada a adequação geral do modelo (67).

O desenvolvimento de intervenções complexas também deve ser guiado por determinados princípios. A diretriz do UK Medical Research Council destaca que a pesquisa em intervenções complexas é desenvolvida ao longo de diferentes fases e deve considerar elementos centrais, tais como o contexto, o refinamento da teoria, o engajamento das partes interessadas, a identificação de incertezas, o refinamento da intervenção e as condições econômicas (68).

O embasamento teórico descrito possibilitou o desenvolvimento da teoria apresentada nesta tese, que inclui um novo modelo de mente. Embora tenham surgido novas propostas de classificações diagnósticas na Psiquiatria, ainda não há um modelo do funcionamento da mente que seja amplamente utilizado. Alguns modelos já foram propostos, contudo, frequentemente não é possível testá-los da forma mais adequada. Além disso, a ausência de um modelo de mente compatível com os avanços atuais da neurociência é um obstáculo para uma avaliação mais precisa e uniforme de emoções, comportamentos e pensamentos associados aos transtornos psiquiátricos.

O termo “mente predostática”, uma combinação dos termos “predição” e “homeostase”, descreve os mecanismos preditivos pelos quais os indivíduos avaliam estímulos ambientais e buscam alcançar o equilíbrio. A homeostase é um processo que permite que os sistemas fisiológicos mantenham sua estabilidade enquanto se adaptam a condições externas em constante mudança. Cannon propôs que a homeostase é um resultado da evolução, que permitiu ao corpo desenvolver a capacidade de reagir a mudanças no ambiente por meio de respostas emocionais e comportamentais (69). Em essência, os organismos vivos evoluíram para manter um ambiente interno estável. Cabe ressaltar que a homeostase não é um estado

estático, mas, sim, um processo dinâmico mediado por respostas internas e externas (70). O equilíbrio homeostático é mantido por meio de mecanismos de feedback e feedforward, que promovem a autorregulação em sistemas biológicos e têm importante interação com estímulos ambientais (36,71).

Uma nova perspectiva no debate sobre mente passou a sugerir que o sistema nervoso funciona com base na predição probabilística, buscando minimizar a disparidade entre as expectativas do organismo em relação ao ambiente e as evidências fornecidas pelos sentidos. Dessa forma, a chamada “mente preditiva” poderia utilizar seu conhecimento de padrões e experiências perceptivas para antecipar eventos (72).

De acordo com teorias atuais, o comportamento também pode ser visto como uma resposta homeostática a estímulos ambientais. Comportamentos direcionados a objetivos podem resultar de previsões. As reações de luta e fuga, presentes inclusive em animais menos complexos, também podem ser uma consequência de predições de risco. Em humanos, o cérebro, como principal centro de processamento de informações, desempenha um papel crucial na coordenação e integração das ações realizadas por diferentes partes do corpo (73).

A compreensão das adições a partir da teoria de que a mente funciona com base em predições proporciona uma explicação nova para o surgimento e manutenção desses transtornos. A partir desse modelo, é possível compreender melhor as relações entre estímulos ambientais, comportamentos, emoções e sintomas associados aos transtornos aditivos.

3 JUSTIFICATIVA

Apesar do avanço da pesquisa na área das adições, ainda há limitações no diagnóstico, na compreensão etiológica e, sobretudo, na efetividade dos tratamentos. As abordagens atuais têm demonstrado aplicabilidade clínica restrita, baixa adesão dos pacientes e efetividade baixa ou moderada, especialmente em casos mais complexos. Os transtornos aditivos têm mantido alta prevalência na população, além de estarem associados a uma significativa carga de doença.

Observa-se a necessidade de uma abordagem mais integrada, dinâmica e transdisciplinar para compreender e tratar os transtornos aditivos, tendo em vista que os avanços terapêuticos parecem não acompanhar o aumento da prevalência, ao contrário do que ocorre na oncologia, por exemplo. Os modelos mais tradicionais de classificação diagnóstica têm falhado em abarcar a diversidade de fatores biológicos, psicológicos e sociais que estão na origem desses transtornos, o que dificulta a compreensão por parte dos pacientes e inclusive dos terapeutas. Esses aspectos ressaltam a importância de desenvolver e propor novos modelos teóricos, como o modelo da “mente predostática”, proposto nesta tese. O conceito de "mente predostática", que apresenta uma lógica um pouco mais simples, clara e testável, surge como uma perspectiva de ampliar a compreensão das adições e possibilitar o desenvolvimento futuro de novas estratégias de tratamento. Este conceito é aplicado em um modelo de avaliação transdiagnóstico, que compreende a adição como um conjunto de manifestações clínicas distintas, em dimensões que costumam estar associadas a sofrimento e prejuízo para si e/ou para outros.

A alta heterogeneidade dos pacientes com transtornos aditivos sinaliza a necessidade de tratamentos que contemplem diferentes sintomas. Adicionalmente, a adição pode afetar diversos domínios da vida do indivíduo, que também devem ser abordados por meio de intervenções psicossociais. O campo das adições, assim como outras áreas da psiquiatria, poderia se beneficiar de uma abordagem alinhada à psiquiatria de precisão, que se propõe a desenvolver tratamentos mais personalizados. Portanto, esta tese se justifica pelo objetivo de promover novas discussões e conceitos teóricos, propor um modelo transdiagnóstico de avaliação e também intervenções práticas na área das adições.

4 OBJETIVOS

4.1 OBJETIVO GERAL

Desenvolver um modelo integrativo, dinâmico e transdiagnóstico a ser aplicado na avaliação e no tratamento de pacientes com transtornos aditivos. Inicialmente, o modelo proposto é mais direcionado aos transtornos por uso de substâncias.

4.2 OBJETIVOS ESPECÍFICOS

a) Descrever o modelo da mente predostática, um modelo de mente transdiagnóstico para o campo das adições.
b) Descrever um modelo de avaliação e diagnóstico de adições, baseado nos conceitos da mente predostática.
c) Desenvolver uma proposta de organização do tratamento, incluindo intervenções farmacológicas e não farmacológicas, com base nesse modelo de diagnóstico e nos conceitos da psiquiatria de precisão.
d) Sugerir potenciais aplicações clínicas para futuramente validar as propostas com análises quantitativas ou mesmo testes em animais.

5 MÉTODOS

5.1 REVISÃO DA LITERATURA

Esta tese foi desenvolvida a partir de uma abordagem metodológica de construção teórica integrativa, orientada por síntese narrativa estruturada da literatura científica, integração translacional de evidências e desenvolvimento progressivo de modelos conceituais aplicados aos transtornos aditivos. Considerando a complexidade, heterogeneidade clínica e natureza multifatorial das adições, optou-se por uma metodologia capaz de integrar evidências provenientes de diferentes níveis de análise (neurobiológico, psicológico, cognitivo, emocional, comportamental, ambiental e clínico) com o objetivo de desenvolver um modelo transdiagnóstico e dimensional aplicável à prática clínica contemporânea.

A construção teórica da tese foi baseada em princípios contemporâneos de *theory building* em saúde mental, segundo os quais modelos complexos devem emergir da integração progressiva entre observações clínicas, fenômenos empíricos, hipóteses mecanísticas e plausibilidade conceitual. Nesse contexto, a tese não teve como objetivo testar uma hipótese isolada, mas propor um modelo integrativo capaz de organizar diferentes dimensões associadas às adições dentro de uma lógica regulatória, dinâmica e transdiagnóstica. O desenvolvimento conceitual foi influenciado por modelos contemporâneos de psiquiatria dimensional e transdiagnóstica, incluindo perspectivas relacionadas ao RDoC, HiTOP, psiquiatria de precisão, neurociência das adições e modelos baseados em sistemas regulatórios e processamento preditivo.

Foi realizada uma revisão narrativa estruturada da literatura científica nas bases MEDLINE/PubMed, SciELO, LILACS e Web of Science, complementada por busca manual de referências consideradas relevantes para os temas centrais da tese. As estratégias de busca incluíram descritores relacionados a transtornos aditivos, transdiagnosticidade, regulação emocional, impulsividade, compulsividade, controle cognitivo, neurobiologia do estresse, processamento de recompensa, homeostase, processamento preditivo, psicoterapia, psicofarmacologia, psiquiatria dimensional e psiquiatria de precisão. Também foram incluídos estudos envolvendo mecanismos neurobiológicos relacionados aos sistemas dopaminérgico, glutamatérgico, opioide, serotoninérgico e noradrenérgico, além de pesquisas sobre

intervenções psicossociais, funcionamento executivo, aprendizagem comportamental, tomada de decisão, interocepção e vulnerabilidades transdiagnósticas.

A seleção dos estudos ocorreu de maneira intencional e orientada pela relevância conceitual, clínica e mecanística para os modelos propostos. Foram priorizados artigos de revisão, estudos translacionais, ensaios clínicos, investigações neurobiológicas, modelos teóricos, estudos dimensionais em psiquiatria e publicações relacionadas a tratamentos baseados em evidências em adições e transtornos mentais correlatos. Considerando o caráter teórico-conceitual e integrativo da tese, a heterogeneidade metodológica dos estudos incluídos impossibilitou a realização de metanálise ou revisão sistemática quantitativa, tornando mais apropriada a utilização de uma síntese narrativa estruturada e interpretativa.

5.2 A CONSTRUÇÃO DO MODELO DOS TRÊS MODOS DA MENTE PREDOSTÁTICA

O desenvolvimento da tese ocorreu de maneira progressiva e cumulativa ao longo de artigos interdependentes que contribuíram para a formulação gradual dos modelos conceituais apresentados. Inicialmente, foi proposto um modelo centrado em regulação cognitivo-emocional das adições, organizando sintomas e intervenções em dimensões clínicas relacionadas à desregulação emocional, impulsividade, compulsividade e sofrimento psíquico. Posteriormente, a formulação evoluiu para o modelo DREXI3 (Dysregulation Phenomena of the Three Main Modes of the Predostatic Mind), que propõe compreender os transtornos aditivos como padrões crônicos de desregulação envolvendo três modos funcionais principais da mente: Alarm Mode, Seek Mode e Balance Mode.

O termo “mente predostática” surgiu da combinação dos conceitos de “predição” e “homeostase”, a partir da revisão da literatura sobre teorias no campo das adições que destacam o papel da regulação. Brüne et al. também sugeriu que os diagnósticos em Psiquiatria deveriam abarcar aspectos evolucionistas do comportamento (74). Ao mesmo tempo, os modelos biológicos dos transtornos aditivos contribuíram para o entendimento de que o comportamento pode ser influenciado pela expectativa de riscos ou recompensas. Integrando esses conceitos, foi proposto que a mente funcionaria entre três modos principais: alarme, busca e equilíbrio, que abarcariam, de uma forma reducionista, os trê sistemas básicos do organismo, que seriam “threat system” (ameaça), “drive system” (recompensa) e “soothing system" (acalmamento).

Com o objetivo de facilitar a identificação de sintomas relacionados a essas predições de risco, foram propostos inicialmente seis domínios de sintomas relacionados à adição:

alterações neurofisiológicas; impulsividade; compulsão; prejuízo cognitivo/psicose; humor; ansiedade/raiva. Dessa forma, a avaliação de pacientes com transtornos aditivos incluiria a quantificação de sintomas em cada um desses domínios.

5.3 A CONSTRUÇÃO DE UM MODELO DE TRATAMENTO

A partir de uma revisão da literatura conduzida de forma estruturada e voltada principalmente para intervenções transdiagnósticas não-farmacológicas, foi elaborada a proposta de um novo modelo de tratamento para os transtornos por uso de substâncias. Embora já existam tratamentos farmacológicos e psicossociais embasados por evidências, constatou-se a necessidade de selecionar e organizar as intervenções de forma mais direcionada e personalizada conforme os sintomas apresentados por cada paciente.

O framework terapêutico BE-CERTIF(AI)D foi desenvolvido como extensão clínica e operacional dos princípios do DREXI3, organizando estratégias terapêuticas em múltiplos domínios transdiagnósticos relacionados à regulação comportamental, ambiental, cognitiva, emocional, neurofisiológica, neuropsicológica, identidade, objetivos futuros e intervenções orientadas por dados e inteligência artificial. O modelo buscou integrar psicoterapia, psicofarmacologia, fatores ambientais, monitoramento dimensional e princípios de personalização terapêutica dentro de uma lógica regulatória compartilhada.

Considerando a complexidade dos pacientes para os quais essa proposta foi pensada, o número de dimensões de sintomas foi ampliado de seis para vinte: apetite, sono, energia, libido, dor, volição, impulsividade, conexão social, compulsão, anorexia, atenção, memória, sensopercepção, orientação, consciência, euforia, tristeza, agressividade, irritabilidade e ansiedade. Foram elaborados instrumentos que permitem a quantificação dos sintomas relacionados a esses domínios e as potenciais intervenções farmacológicas e psicossociais a serem utilizadas. As intervenções psicossociais para cada domínio regulatório foram organizadas para serem aplicadas aos seguintes grupos: desregulações comportamentais, desregulações ambientais, desregulações cognitivas, desregulações emocionais e desregulações neurofisiológicas e neuropsicológicas. Para a aplicação clínica deste modelo, na forma de um instrumento foi proposto um algoritmo que contempla a avaliação do perfil de desregulação, a organização da lógica avaliativa, a avaliação de cada domínio de desregulação e o mapeamento de intervenções psicoterapêuticas e psicossociais e de intervenções farmacológicas.

Paralelamente ao desenvolvimento conceitual desta tese, foi elaborado, no mesmo centro de pesquisa, um instrumento dimensional denominado TDPM-20 (Transdiagnostic Dysregulation of the Predostatic Mind – 20 Dimensions), desenvolvido por pesquisadora vinculada ao grupo de pesquisa em álcool e drogas do HCPA/UFRGS, com o objetivo de operacionalizar clinicamente os construtos derivados do modelo DREXI3/ACERT. Embora o instrumento dialogue teoricamente com os modelos apresentados nesta tese, sua construção metodológica ocorreu de forma paralela e independente, não constituindo objeto central desta investigação.

O desenvolvimento inicial do TDPM-20 ocorreu a partir de uma abordagem teórico-conceitual e clinicamente orientada, baseada na síntese da literatura sobre modelos transdiagnósticos, neurobiologia das adições, regulação emocional, impulsividade, compulsividade, funcionamento executivo, sintomas internalizantes e externalizantes e mecanismos relacionados aos sistemas de ameaça, recompensa e autorregulação. A construção do instrumento também foi fundamentada na observação clínica de padrões recorrentes de desregulação em pacientes com transtornos aditivos acompanhados em contextos assistenciais especializados. As vinte dimensões propostas foram organizadas com o objetivo de representar domínios clinicamente observáveis associados aos modos Alarm, Seek e Balance descritos no modelo DREXI3, buscando auxiliar futuramente na avaliação dimensional, estratificação clínica e personalização terapêutica.

Em sua versão inicial, o TDPM-20 foi concebido como uma entrevista clínica semiestruturada de caráter exploratório e translacional, destinada prioritariamente à organização clínica e à geração de hipóteses para futuras validações psicométricas, longitudinais e neurobiológicas. Dessa forma, o instrumento é apresentado nesta tese apenas como um modelo complementar e potencialmente útil para operacionalização futura dos construtos teóricos discutidos, não sendo tratado como instrumento validado nem como produto metodológico principal desta investigação.

A organização final dos modelos propostos considerou critérios de coerência clínica, plausibilidade neurobiológica, integração transdiagnóstica e aplicabilidade terapêutica. As dimensões incluídas foram estruturadas a partir da identificação de padrões clínicos recorrentes descritos na literatura e observados em contextos assistenciais especializados, particularmente relacionados a impulsividade, compulsividade, sofrimento emocional, alterações neurofisiológicas, prejuízos cognitivos, hipersensibilidade ao estresse, déficits de autorregulação e vulnerabilidades motivacionais. Buscou-se integrar esses domínios dentro de uma lógica regulatória dinâmica, compreendendo os transtornos aditivos não como entidades

isoladas, mas como manifestações heterogêneas de processos parcialmente compartilhados de desregulação.

Por fim, esta tese adota a perspectiva de que modelos teóricos em psiquiatria devem ser compreendidos como estruturas abertas, dinâmicas e passíveis de refinamento progressivo mediante futuras validações clínicas, psicométricas, neurobiológicas e longitudinais. Dessa forma, os modelos DREXI3, BE-CERTIF(AI)D e TDPM-20 são apresentados como propostas conceituais integrativas destinadas a aproximar neurociência, psicopatologia, psicoterapia, psicofarmacologia e tomada de decisão clínica dentro de uma lógica regulatória transdiagnóstica compartilhada, com potencial aplicabilidade futura em contextos de psiquiatria personalizada e medicina de precisão.

6 ARTIGOS

Nesta seção, serão apresentados os artigos com os resultados e a discussão do trabalho desenvolvido nesta tese.

6.1 ARTIGO 1

Editorial publicado na *Advances in Clinical Toxicology*, traz uma proposta inicial de um modelo de avaliação, medidas e tratamento das adições.

ADVANCED COGNITIVE EMOTIONAL REGULATION THERAPY (ACERT) FOR ADDICTION TREATMENT

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Editorial

The last decades have shown relevant improvement in the therapeutic strategies aimed at psychiatric symptoms; however, addiction treatment remains unclear and controversial. Although there are specific medications approved for treating alcohol and opioid abusers, the consumption of these and other drugs is still high along with their severe consequences [1]. Pharmacological therapies for other substance use disorders are still in need, while their prevalence increases in many countries, as well as its burden of disease [2]. Currently, the ideal treatment for addiction involves a multidisciplinary team and combines pharmacological strategies, psychotherapy and contingency management aimed at reinforcing more adaptive behaviors. Considering pharmacological strategies for drug abuse, they are usually focused on symptoms such as craving - a subjective cognitive (desire thoughts) and emotional (arousal feelings) that is hard to validate. There is no consensus on how to define,

measure and treat craving, since substance abusers are a heterogeneous population with different psychiatric comorbidities and personality disorders. Nevertheless, treatment of psychiatric symptoms (e.g.. anxiety and depression) with medications reduces drug use in clinical trials with samples composed of alcohol or drug addicts [3-6].

Several hypotheses about the development of addiction have been studied in the last years. Among others, the Self-Medication Hypothesis gained considerable traction by the time of its initial publications. It was grounded on the assumption that drugs could relieve pre-existing psychological suffering and that there is some specificity in a person's drug of choice [7]. Although this hypothesis derives mainly from clinical observation and subsequent studies raised questions about its validity, it turned into a relevant paradigm in the field of addictions [8].

Other theoretical models have documented a strong connection between emotional dysregulation, addictive behaviors and psychopathology among general and clinical samples. Emotional regulation strategies can be portrayed as automated or controlled methods used to cope with or modify the external expression and/or internal experiences. They are utilized when emotional states have unwanted impact on a desired outcome, and can be broadly described as aiming at adaptive or maladaptive strategies [9]. Research suggests that emotional dysregulation can act as a moderator between environmental factors - such as stressful events, and problematic substance use. However, longitudinal studies are needed to determine causality, as the use of drugs can also impact the ability to cope with negative affects [10]. Alexithymia has already been cited as a possible risk factor for substance use disorders [11], which shows the importance of evaluating cognitive aspects in addiction; since alexithymia may complicate subjective emotional states investigation using only questionnaires.

Most psychopharmacological studies in the addiction field focus their aims at specific systems, receptors or brain regions related to seeking behavior and self-control; they usually fall short in the real world due to the existence of stressful events and cue eliciting craving situations, which directly affect the regulation of emotional states, and are rarely reproducible in such studies. Currently, most clinical trials use objective outcomes – such as the amount of substance use and frequency of consumption in order to evaluate treatment improvement and medication efficacy.

Thus, although there are different classification systems in psychiatry - categorical and dimensional ones [12,13], there is still a need for a logical framework that could help clinicians and pharmacotherapists project the evaluation and treatment of addicted patients using Emotional Regulation theories. In this sense, this Brief Communication aims to propose

a model to organize, measure and treat addictions from the perspective of regulation of emotional and cognitive aspects of the mind with pharmacological and psychotherapeutic strategies.

Advanced Cognitive Emotional Regulation Therapy (ACERT)

The treatment framework proposed here originates from symptomatological dimensions commonly used in pharmacological and psychotherapeutic treatment in psychiatry [14]. The development of this model was based on the clinical experience of the authors in the addiction field along with a literature review, and took into consideration the main neurobiological systems that support the theoretical rationale for psychopharmacological therapeutic plans and algorithms used for psychiatric disorders.

First, it is relevant to mention that patients undergoing cognitive emotional interventions cannot be intoxicated in order to avoid confounding their withdrawal symptoms with psychiatric disorders. The main rationale of the model is that craving and addictive seeking behaviors are respectively internalized and externalized responses of the brain-mind complex in order to regulate cognitive and emotional signs. They are usually associated with stress, with the goal of reaching homeostasis or Wellness [15,16]. As shown in Figure 1.

Our idea is that clinicians should assess symptomatology in the four poles in order to reduce craving and addictive symptoms, aiming at the "core" of the diagram (in pink). For each of these dimensions and poles, there are specific psychopharmacological options, commonly divided in categories as antipsychotics, antidepressants,mood stabilizers, benzodiazepines and stimulants. Some medications may be in more than one category and many patients will need more than two or three to achieve a good cognitive emotional regulation. For example, depression can be treated with antidepressant and additional agents such as mood stabilizers and atypical antipsychotics. The model infers intersections between dimensions which represent symptoms presented in different disorders (eg. irritability) that could be treated with similar medications. In order to organize pharmacotherapy and psychotherapy options, each dimension or intersection (represented by different colors) may correspond to different classes of psychotropic drugs, such as antipsychotics, antidepressants, mood stabilizers and stimulants.

As shown in Figure 2, a spider graph portrays the varying degrees of symptoms in each group on a scale from 0 to 10; we present 3 case examples of different dimension dysregulation according to the patients' psychiatric and personality characteristics. These would guide a more efficacious pharmacological and psychotherapeutic treatment plan. This

new paradigm suggests that a more complex combination of medications could help achieve a higher cognitive emotional regulation impacting on drug- seeking behavior. We suggest that during treatment initiation symptom regulation should target more than 70% of improvement, which is the usual goal of psychiatric studies.

In future research, measurement instruments can be developed to investigate patients' symptoms severity in each of the six dimensions. Therefore, interventions targeting reduction of specific symptomatology can be properly tested. We postulate that reducing symptoms related to anxiety, mood dysregulation, psychosis, impulsivity and physiologic dysregulation will consequently decrease craving, which is associated with drug-seeking behavior and other symptoms of compulsive addiction disorders. Besides pharmacological interventions focused on signs and symptoms, this treatment model may include psychotherapy techniques such as Motivational Interviewing, Cognitive Behavioral Therapy (CBT), Relapse Prevention, Emotional Regulation Training and Mindfulness, for example. They are usually effective to regulate emotional and behavioral responses, with fewer side effects, especially in long-term treatments. Psychotherapies play an essential role in addiction treatment. The choice of a specific psychotherapy is in line with scientific evidence about addiction treatment, which supports CBT and neuropsychological interventions for improving decision- making deficits and altering response to drug-related cues [17]. However, recent literature also proposes a more integrative approach to addiction psychotherapy, adding new concepts to the theory of self-medication [18].

Besides emotional and cognitive regulation - which may reduce craving and drug-seeking behavior, most substance abusers and other types of addicted patients usually present past and current stressful events (socioeconomic, relationships, work) that should be also evaluated and addressed in order to decrease the source of dysregulation and maladaptive responses. One of the most useful instruments for this purpose is the Addiction Severity Index [19,20]. Thus, this proposed model could be a complementary tool to help organize, evaluate and define the best pharmacological and psychotherapeutic practices aimed at addicted patients.

Conclusion

This Brief Communication emphasized the need for new paradigms in the field of addictions to cover the inherent complexities that occur in treatment modalities. We described a model with both biological and psychological aspects of substance use disorders and proposed an integrative intervention. Especially in this field, drug users can be extremely heterogeneous in terms of psychiatric comorbidities and socio demographic profile. Therefore, clinical trials

with broad interventions combining multiple medications and different psychotherapeutic techniques can be quite expensive and difficult to develop, since it is hard to define which intervention led to an expected outcome or to an adverse effect. Moreover, clinical trials have been targeting medications related to the Reward System instead of interventions that could reduce psychological (cognition and emotion) suffering that could be designed regardless of the underlying specific mechanism of action since medications achieve different results and adverse effects in this population.

It is time to evolve in the direction of more complex studies with multiple assessments and tailored strategies and interventions centered in cognitive emotional regulation that seem to be useful and intelligible for most health professionals by helping improve behavioral control. Future research with adequate methodology must analyze and validate these propositions - which could be a game changer - and enhance strategies to evaluate and treat addiction. The authors also seek international collaboration in order to keep developing this innovative, transdiagnostic and user-friendly treatment model.

References

1. Peacock A, Leung J, Larney S, Colledge S, Hickman M, et al. (2018) Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction 113(10): 1905-1926.

2. Charlson FJ, Baxter AJ, Cheng HG, Shidhaye R, Whiteford HA (2016) The burden of mental, neurological, and substance use disorders in China and India: A systematic analysis of community representative epidemiological studies. Lancet 388(10042): 376-389.

3. Han DH, Kim SM, Choi JE, Min KJ, Renshaw PF (2013) Adjunctive aripiprazole therapy with escitalopram in patients with co-morbid major depressive disorder and alcohol dependence: Clinical and neuroimaging evidence. Journal of Psychopharmacology 27(3): 282-291.

4. Martinotti G, Andreoli S, Di Nicola M, Di Giannantonio M, Sarchiapone M, et al. (2008) Quetiapine decreases alcohol consumption, craving, and psychiatric symptoms in dually diagnosed alcoholics. Hum Psychopharmacol 23(5): 417-424.

5. McGrath PJ (1996) Imipramine Treatment of Alcoholics with Primary Depression: A Placebo-Controlled Clinical Trial. Arch Gen Psychiatry 53(3): 232-240.

6. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, et al. (2005) Efficacy of Valproate Maintenance in Patients With Bipolar Disorder and Alcoholism. Arch Gen Psychiatry 62: 37-45.

7. Khantzian J (1985) Focus on Heroin and Cocaine Dependence. Am J Psychiatry 6.

8. Khantzian EJ (1997) The Self-Medication Hypothesis of Substance Use Disorders: A Reconsideration and Recent Applications. Harv Rev *Psychiatry* 4(5): 231-244.

9. Leppanen J, Brown D, McLinden H, Tchanturia K, Williams S (2021) The role of emotion regulation in eating disorders: A network meta-analysis approach. Front Psychiatry 13: 793094.

10. Cavalli JM, Cservenka A (2021) Emotion Dysregulation Moderates the Association Between Stress and Problematic Cannabis Use. Front Psychiatry 11: 597789.

11. Orsolini L (2020) Unable to Describe My Feelings and Emotions without an Addiction: The Interdependency between Alexithymia and Addictions. Front Psychiatry 11: 543346.

12. Goldberg LR (1993) The Structure of Phenotypic Personality Traits. American Psychologist, pp: 9.

13. Watson D, Levin-Aspenson HF, Waszczuk MA, Conway CC, Dalgleish T, et al. (2022) Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): III. Emotional dysfunction superspectrum. World Psychiatry 21(1): 26-54.

14. Kessler FHP, Marchi N, Ornell F, Scherer JN, Sordi AO, et al. (2019) Advanced Cognitive Emotional Regulation Therapy (ACERT) for Addiction Treatment. 14th World Congress of Biological Psychiatry, Vancouver, Canada.

15. Alexander AC, Waring JJC, Olurotimi O, Kurien J, Noble B, et al. (2022) The relations between discrimination, stressful life events, and substance use among adults experiencing homelessness. Stress Health 38(1): 79-89.

16. Garke MA, Isacsson NH, Sörman K, Bjureberg J, Hellner C, et al. (2021) Emotion dysregulation across levels of substance use. Psychiatry Res 296: 113662.

17. Verdejo-García A, Alcázar-Córcoles MA, Albein-Urios N (2019) Neuropsychological Interventions for Decision- Making in Addiction: A Systematic Review. Neuropsychol Rev 29(1): 79-92.

18. Feingold D, Tzur Bitan D (2022) Addiction Psychotherapy: Going Beyond Self-Medication. Front Psychiatry 13: 820660.

19. McLellan TA, Cacciola JC, Alterman AI, Rikoon SH, Carise D (2006) The Addiction Severity Index at 25: Origins, Contributions and Transitions. Am J Addict 15(2): 113- 124.

20. Kessler F, Cacciola J, Alterman A, Faller S, Souza-Formigoni ML, et al. (2012) Psychometric properties of the sixth version of the Addiction Severity Index (ASI-6) in Brazil. Braz J Psychiatry 34(1): 24-33.

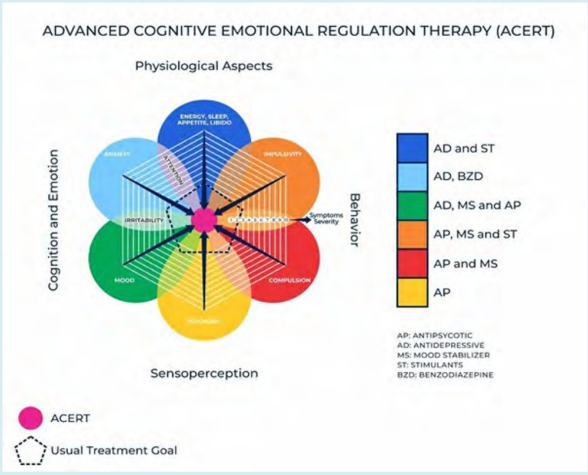


Figure 1: Six dimensions of symptoms identified by different colors are suggested to be used in this model: psychosis, anxiety, mood, neurophysiological aspects (ex. energy, sleep, and appetite), impulsivity and compulsion. These categories are allocated in four areas: physiological aspects, cognition and emotion behavior and sensoperception.

Figure 1.

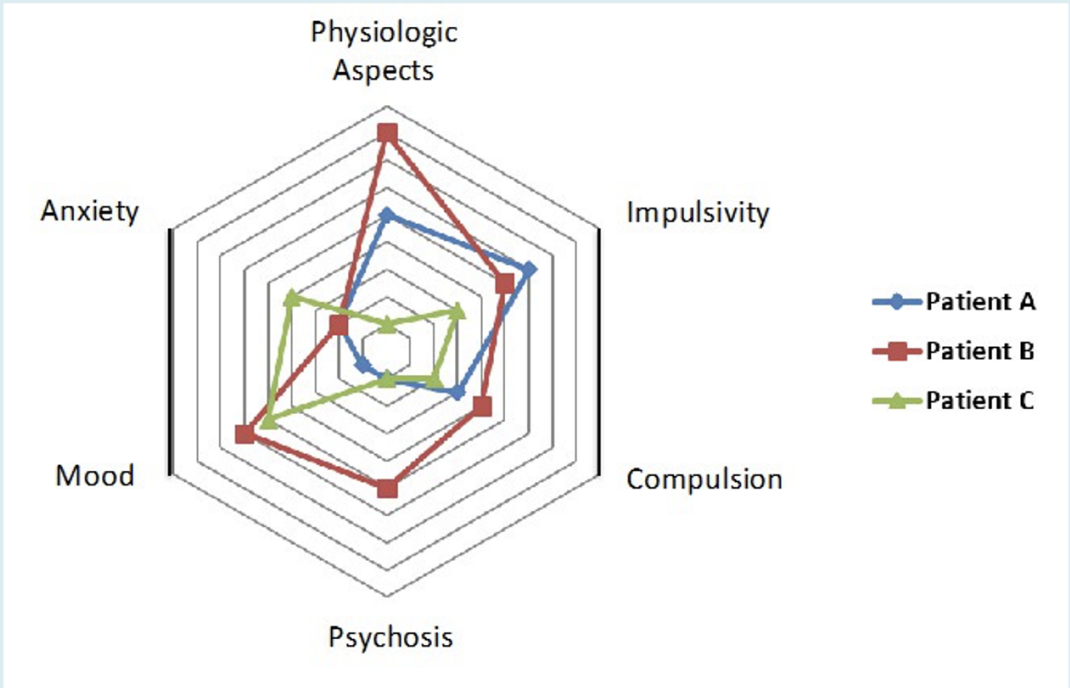


Figure 2: Clinical patient examples of Addiction Evaluation based on ACERT dimensions.

Figure 2.

6.2 ARTIGO 2

Artigo publicado na *Frontiers in Psychiatry* (fator de impacto 3.2), atualmente com 5 citações, traz uma descrição mais completa deste modelo baseado em um novo paradigma.

PROPOSING AN INTEGRATIVE, DYNAMIC AND TRANSDIAGNOSTIC MODEL FOR ADDICTIONS: DYSREGULATION PHENOMENA OF THE THREE MAIN MODES OF THE PREDOSTATIC MIND

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1 Introduction

Addictive behaviors, especially drug use disorders, have become more prevalent in the 21st century. According to the World Drug Report, the worldwide number of people who reported having used drugs within the last 12 months was higher in 2020 versus in 2010 (1). In addition to the high prevalence rates, the burden of addictive disorders is significant. Around the world, deaths from substance use disorders rose from 284,000 in 2007 to 352,000 in 2017 according to the Global Burden of Disease Study (2). For instance, alcohol and drug use disorders are among the main mental health-related causes of disability-adjusted life years in the last decades (3). Even though substances of misuse have different neurochemical

profiles, addictive behaviors (directed toward a drug or behavior) usually have a common phenotype.

Despite the relevance of this topic, divergences and controversies can be found in the literature regarding the nature of addictive disorders, the concept of addiction, and even the diagnosis of these conditions, which ultimately have a negative impact on the development of effective preventive and treatment interventions. In this sense, several potential strategies aimed at improving the quality of life of these patients show poor effectiveness, leading to a lack of consensus about clinical recommendations in the field. Moreover, current therapeutic interventions tend to show low compliance rates and small to moderate effect sizes even for best-practice treatment options (4–6).

Distinct theories have been proposed to explain the mechanisms that lead to addiction. Neurobiological and neuroimaging research has drawn attention to biological theories, with evidence supporting the role of rewarding neural pathways, especially the ones related to dopamine, in seeking behavior and reward (7). Conversely, reflexive choice theories state that individuals can consciously choose to engage in addictive behaviors (8, 9), whereas the self-medication hypothesis, proposed by Khantzian, claims that individuals are predisposed to addiction because of negative affect states and comorbid psychiatric disorders; in this mental scenario, the effect of the drug of choice - as well as the individual's perception of some type of control over his/her inner feelings would balance the prevailing negative emotion (10). This latter hypothesis has been reviewed by its author, associating specific substances with psychiatric comorbidities, with conflicting evidence (some supporting and some weighing against the theory) (11).

Some authors have tried to explain addictive behaviors and emotions from different perspectives. The automatic processing theories, for instance, propose that addictive behaviors can be acquired without self-conscious intentions (12–15). Goal-focused theories, in turn, have tried to explain addiction by relating its development with the seeking of positive rewards or the avoidance of negative emotions – these include the drug withdrawal theory, which defines addiction as the physiological adaptation and resulting withdrawal symptoms that occur as a consequence of drug use (16). In recent years, theories focusing on the individual have tended to describe addiction as the result of a combination of factors, mainly environment and internal characteristics – therefore, they are called integrative theories (17–19). One example is the PRIME theory, by Robert West, which attempted to integrate features of different models of addiction in a single model. According to that model, motivation should be a common aspect in addiction theories (20).

Another category of theories tries to explain addiction at a population level. Social network theories, for example, propose that the prevalence of addiction in a population is related to the connections between individuals with and without addictive behaviors (21, 22). Economic models state that addictive behaviors can be predicted by functions (23, 24). Communication theories focus on marketing activities as having a great influence on patients with addiction, which are considered "consumers" (25, 26). Furthermore, the organizational system model understands addictive behaviors as an interaction between different elements of a society (27, 28). In addition to a dispute across research lines suggesting that the phenomena of addiction are related to brain disease, choice disorder, or a learning process (29), the diagnostic criteria of addiction in existing manuals have also raised discussion.

Currently, the clinical diagnosis of substance use disorder is generally based on categorical entities originating from classification systems (30). Even though classification systems such as the DSM-5 and ICD-11 have made significant contributions in terms of providing reliability for diagnostic procedures - which ultimately serve as the basis for clinical assessment, treatment-decision, scientific investigation, and public health policies, they are also often the object of criticism. Much has been discussed about the potential of medicalization of aspects and issues of daily life. Moreover, categorical diagnostic entities in those classification systems are usually not based on strong scientific evidence or neuroscientific concepts (30, 31). Recent studies have examined the limitations of categorical systems in assessing psychopathology (32), which also impacts the field of addiction. Translating diagnostic criteria of addiction into terms of quantitative behavioral processes could expand the possibilities of how this disorder is understood and treated (33). The Research Domain Criteria (RDoC) framework was especially designed for pathophysiology research (34), while the Hierarchical Taxonomy of Psychopathology (HiTOP) system seeks to improve the organization of psychopathology, phenomenology, illness course, and treatment response, both in research and clinical practice (35). Both these dimensional approaches have strengths that could be complementary and promote the development of new frameworks (36).

When examining the relationship between different types of addictive disorders, i.e., behavioral and substance addictions, more similarities than differences can be found. Both types of addiction tend to emerge in late teenage years or early adulthood and follow a course of lapses and recoveries. The risk factors are also similar, potentially including adverse childhood experiences, neurobiological dysregulation, low distress tolerance, and emotional dysregulation. Moreover, both behavioral and substance addictions share common clinical

processes that may be targeted in treatment. Nevertheless, because categorical classifications have proven insufficient, new frameworks tend to adopt a symptomatologic perspective (37).

Bickel et al. emphasize that distinct theories may each provide a perspective on how to conceptualize addiction, but the disorder may be the result of different processes, or one symptom may be caused by distinct mechanisms, which poses a diagnostic approach challenge
(33). Some other authors have been pointing to a translational crisis in the addiction field: although basic research has identified some neurological basis for addiction, the impact of these findings on clinical practice has been limited (38, 39). Research with animal models self-administering drugs has been conducted for many years, aiming to improve the understanding of a biological basis of addiction
(40). However, the advances in basic research have not led to equivalent developments in therapeutic strategies. This translational failure shows the need for changes in this research field as well as in other areas within psychiatry (41).

It becomes fundamental to have a well grounded conceptual model that contemplates these patterns of emotions, thoughts, and especially behaviors. In the present paper, the authors propose a novel theoretical-clinical model to explain the phenomena of addiction from a more integrative perspective. The proposed model will be presented and its fundamental aspects discussed in light of the most relevant theories and recent paradigms in science.

2 The predostatic mind

The main purpose of living beings is to achieve homeostasis, which is defined as a self-regulating process by which physiological systems maintain stability while adapting to changing external conditions (42). Cannon suggested that homeostasis is the summit of countless years of evolution, by which the body reacts to changes in the environment with emotional and behavioral responses (43). In other words, living systems evolved to maintain a stable internal environment in order not to be destroyed by the forces surrounding them. It is clear that homeostasis is not static; rather, it is a dynamic self-adjusting process mediated by stimuli and internal and/or behavioral responses (44).

Homeostasis is accomplished by mechanisms of feedback and feedforward and could explain self-regulation in biological systems (42, 45). Feedback occurs when outputs of a system are routed back as inputs in a closed loop structure. The past actions of a system are fed into the system to control future actions, acting as the system’s memories. Negative

feedback, in the context of physiological homeostasis of biological systems, is a mechanism that counteracts deviations from a desired state, in order to maintain stability. Positive feedback is characterized as a positive loop gain that produces growth processes. While negative feedback tends to reduce fluctuations in the output, minimizing the effects of disturbances, positive feedback tends to lead to instability via further disorganized behavior. The other mechanism utilized during the homeostasis process, namely feedforward regulation, occurs when the system responds to environmental disturbances in a pre-defined way, adjusting itself before any changes have actually occurred. It requires previous information or memory about the content and magnitude of the stimulus. In living organisms, these memories are provided by learning and experience (42). Survival also depends on the conservation of our body's integrity, and for that it is essential to actively maintain our internal environment – homeostatic equilibrium.

The search for balance is complex in animals – especially humans – and difficult to explain. In this sense, terminology adjustments are needed to facilitate the use of a model in clinical settings or even to describe maladaptive chronic responses that could be considered mental disorders. It is relevant to understand and discuss the mechanisms that living beings use to achieve balance, and we will use the concept of mind as the resulting phenomena of all systems in an organism doing predictive work together to reach this goal. Recently, a new perspective has emerged in the debate involving mind and cognition, according to which the brain and the whole nervous system essentially work as a probabilistic prediction engine, dedicated to the task of minimizing the disparity between how it expects (predicts) the world to be and the evidence presented by the sensory stream (46). The predictive mind uses its knowledge of patterns and perceptual experiences to make predictions about events (47). Therefore, in this paper, we use the novel expression "Predostatic Mind" to better describe the predictive mechanisms by which sensoperception and animal systems evaluate environmental stimuli and try to achieve balance.

According to current theories, besides emotional states and thoughts, behavior is also a homeostatic response to environmental stimuli, and goal-directed behaviors, such as eating or sleeping, may result from predictions. We can think about this in a bidimensional way, where positive and negative predictions may occur, resulting in seek or threat response behaviors. Responses such as fight, flight, and freeze can be seen as a temporary disruption of normal processes aiming at balance. The body's focus shifts from maintaining its internal balance to responding to the immediate threat or stressor. Once the threat is resolved, the body aims to return to homeostasis by restoring normal physiological functioning. This

would be the case in less complex organisms that rely on a simpler sensory apparatus and therefore display a limited number of behaviors. In humans, however, the brain is the main hub of information processing, and the nervous system plays a crucial role in coordinating and integrating actions performed by different parts of the body. Here we must add that all systems operate in the context of the organism as a whole (48). Using environmental cues, stored information (memory and learning) and situational demands, our brain starts calculating the risk associated with the context in which the organism is found. It scans our interior and exterior environments all the time, generating interoceptive and exteroceptive maps (49). According to the predicted risk – low or high, short- or long-term, avoidable or not –, the mind will operate in different modes that are related to patterns of responses in order to achieve goals, such as fight and flight behaviors, to guarantee survival. Different modes will then trigger different responses that are appropriate for each scenario. With regard to homeostatic responses, emerging models have tried to simplify the description of motivations behind animal behaviors. Gilbert, for instance, proposes three main systems of emotional regulation: drive, threat, and soothing. While the latter is commonly related to homeostasis, the systems involved in drive and threat response behaviors are also ways of achieving it (50).

The present paper proposes a model in which addiction is seen as a chronic and maladaptive response of the predictive mind while trying to achieve balance, leading the individual to compulsively seek the same rewarding stimuli (e.g., drug, video game, pornography), despite acute and long-term impairments. Because we want patients to understand the proposed model, the Modes of the Mind will be reduced to three and will be referred to as Alarm Mode, Seek Mode, and Balance Mode. Each of these modes will activate specific neurobiological systems and neurochemicals, as represented in Figure 1, in varied ways. However, the description and explanation of how neurobiological systems activate the modes are not within the scope of this manuscript due to lack of space.

1.1 Alarm mode (threat response systems)

According to the present model, the mind will operate in Alarm Mode when the (imminent and/or severe) risk prediction increases and leads to an increment of stress levels. The disruption of mental prediction involves structures such as the amygdala, the hypothalamus, and the habenula. As the name implies, this mode will be activated when the organism faces a threat, and it will trigger stress-coping behaviors that include freezing, screaming/asking for help, fighting, or flighting. When threat is detected, the sympathetic and parasympathetic

branches of the autonomic nervous system are activated simultaneously, enabling the fast onset of defensive freezing and fight-or-flight responses.

When in Alarm Mode, the individual is vulnerable to imminent or severe risk prediction. It occurs, for example, when a predator is threatening an animal or its offspring. The threatened animal enters the Alarm Mode, which demands a behavior of fighting its opponent. Flight and freeze are other possible responses to achieve self-regulation (51) (or Balance Mode in the proposed model). In the context of drug addiction, the Seek Mode may be activated by stressors that are not solved by alarm responses and lead to drug use in order to achieve balance. However, once the effect of a given substance ends, withdrawal symptoms may activate the threat response systems (or Alarm Mode) again, maintaining addiction. This example is illustrated in Figure 2 and will be discussed in more detail below.

2.1 Seek mode (reward systems)

The Seek Mode is usually defined as the search for pleasant and hedonic stimuli (e.g., psychoactive drugs, sexual and social experiences) that can lead to positive emotions and well-being. However, there is robust evidence that behaviors associated with this mode, such as reproduction and cooperation, are also homeostatic or advantageous for individuals or groups in response to environmental predicted risks. From a neurobiological point of view, this mode is associated with the mesolimbic dopaminergic pathway. It is related to the seeking system described by Wright and Panksepp, namely, a primitive neural system focused on energetic search or conservation of resources among mammals. For example, when an animal is starving, the reward system (Seek Mode) is expected to lead to a highly “obsessive” and focused search for food. Searching for safety and sex is also part of this scenario (52). The Seek Mode includes positive sensations of reward when its demands are fulfilled and the animal can self-regulate again.

This mode can also be associated with success in social and professional (equivalent of hunting) aspects of life. From an evolutionary perspective, the great role of the positive emotions in the Seek Mode would be to improve physical, intellectual, and social abilities so as to promote better adaptation in the long term. In this sense, behaviors related to social connections in some mammals may be linked to positive affect, which is hypothetically associated with hormones such as oxytocin. The orbitofrontal cortex encodes subjective affective valence, which is related to reward in response to a variety of stimuli, whereas the anterior cingulate cortex and its connections with limbic structures, like the amygdala and the

hippocampus, are involved in this homeostatic process through top-down control and emotional regulation. The insula is also involved in this context, as it integrates interoception and emotional conscience (53).

2.2 Balance mode (soothing systems)

The Balance Mode is associated with low risk prediction in present and future perspectives, i.e., it is in place when the individual experiences a state of self-regulation. This is a positive affect state, related to sensations of calmness, rest, contentment – and therefore, behaviors such as sleeping, resting, and relaxing. Depue and Morrone-Strupinsky have demonstrated the existence of a peculiar positive affect system linked to calming, resting, and contentment – a state of quiescence where one is neither under threat nor in a seeking or achieving state of mind, i.e., both the drive and the threat response systems are characterized by calmness (54). Once a goal has been achieved and the animal is not under threat, drive systems need to be "turned off" to rest, produce quiescence, and balance energy expenditure. This system is linked to endorphins and the activation of the parasympathetic nervous system, which is sometimes called a "rest and digest" system (55).

Human and animal research has focused on positive states, which sometimes can be defined as a sensation of calmness and well-being associated with the Balance Mode. The structures involved in well-being include the left prefrontal cortex, which seems to process positive affect and emotions. Opioid release in the amygdala has been reported to diminish its activity during positive emotional experiences in humans (56). Furthermore, the possible role of the Default Mode Network (DMN) in internal regulation should not be overlooked: its involvement in goal-directed tasks like working memory and "introspective behaviors" may be interpreted as an improvement to the internal prediction model. In general attentional states, the DMN would hypomodulate and promote activity in other brain regions responsible for focusing on the external environment. In our homeostatic model, the DMN could hypothetically be related to an internal regulation state, in which the mind works to improve prediction by revising information and memories to adjust predictive models and increase the chance of building more adaptive behavioral responses in the future (57).

3 Addiction as dysregulation based on externalizing and internalizing phenomena of the three main modes of the predostatic mind (DREXI3)

The addiction model proposed by the authors, named dysregulation of the three main modes of the predostatic mind (DREXI3), involves externalizing (behaviors) and internalizing (thoughts and emotions) phenomena. The model describes addiction as a consequence of chronic dysregulation of regulatory systems associated with the three modes described above. Figure 2 shows two types of addiction progression toward a mental disorder according to the idea of different degrees of activation of the modes of the mind. In both examples, the patients begin with greater balance and self-control and progress to significant activation of the Alarm Mode (emotional suffering and threat response behaviors) and the Seek Mode (seek behaviors, although with less positive emotions related to the drug), resulting in low balance and high impairments. According to our model, an interaction between (or simultaneous activation of) the Seek Mode and the Alarm Mode may occur when seeking becomes chronic and leads to a compulsive behavior that fails to achieve balance. The individual may not obtain the desired outcome and experience a state of withdrawal or negative affect (irritability, dysphoria, alexithymia, stress, and lack of motivation for natural rewards).

In the examples, addiction progression results from processes involving chronic and systematic (frequent) activation of the Alarm and Seek Modes, especially in individuals who present some risk factors, such as impulsivity or stressful life events. In some situations, the Alarm Mode may lead to activation of the Seek Mode to achieve internal regulation, particularly when the problem is difficult to solve or when risk prediction is not imminent or related to imminent survival. Drug use only produces a short-duration balance and rarely helps to achieve an adequate response to environmental stimuli, which in turn may trigger the Alarm Mode again. There is a neurobiological basis showing how drug use can affect the prefrontal cortex and impact executive function and decision-making, maintaining addictive behaviors and further impairing self-control in the long term (58). Figure 3 shows the fluctuation between the Alarm and Seek Modes.

Imaging studies conducted with addicted humans have reported that reward brain circuits become less sensitive to natural rewards during states of negative affect. Both the reduction of reward and the increase of stress are cues to the Alarm Mode. In the context of substance use disorders, incentive salience can be developed, linking a cue, e.g., a stressor, to drug use. This state could be interpreted as craving, which consists of worry and anticipation that induce the Seek Mode to find rewarding stimuli in order to achieve regulation. This cue-induced craving is mediated by activation of the prefrontal cortex, including the dorsolateral prefrontal cortex, the anterior cingulate gyrus, and the medial orbitofrontal cortex (58). While in the

threat system the outcomes include fight and freeze, aggravation or hyperactivation of the Seek Mode can lead to intoxication and even death by overdose in cases of substance use disorders.

3.1 Risk prediction, negative reinforcement and addiction

Previous theories of addiction emphasize the search for regulation when facing negative emotions as a determinant factor in addictive behaviors. Jacobs defines addiction as an acquired state of dependence aimed to alleviate stress. His general theory of addiction proposes two determinants for the development of these disorders: existence of an excessively depressed or agitated chronic physiological state; and reaction to adverse experiences early in life. According to that author, the process of addiction would develop in three phases: stage I would be the discovery of the addictive behavior as a potential relief of negative emotions; in stage II, the positive reinforcer of addictive behaviors would make them become compulsive and resistant to change; finally, in stage III, the individual would keep the addictive behavior to avoid negative emotions, in spite of the harm associated (37, 59). The DREXI3 model follows a similar logic, reinforcing the search for balance and self-regulation as a determinant for maintaining the addictive behavior: the Alarm Mode represents an answer to environmental stimuli that cause stress and risk prediction; the addictive behavior then arises with the aim of relief, leading the individual to enter Seek Mode; due to reward prediction and avoidance of negative emotions, the behavior becomes progressively compulsive.

Other theories recently published propose a transdiagnostic treatment model for both substance use disorders and behavioral addictions, considering the similarities between these pathologies. For instance, the addiction components model explains addictive disorders based on these common features, describing six main components: salience, which can manifest as craving; mood changes associated with relief of negative affects; tolerance; abstinence symptoms; conflicts due to the addictive behavior; and relapse (37). Theories like this were also taken into consideration when developing DREXI3, by emphasizing the role of craving (strong and recurrent reward prediction) and the search for self-regulation when facing negative emotions or other internal dysregulations.

Addiction has also been analyzed from an evolutionary perspective. Some characteristics of the addictive process tend to be considered exclusive of mammals and even of humans,

due to their superior cognitive abilities. The neurosystems involved in the search for reward were shaped across evolution to reinforce some behaviors
(60). However, evidence of other animal species that also consume psychoactive substances suggests that the action of the involved systems is not restricted to humans (61, 62). For the scope of DREXI3, addiction is seen as a result of phenomena related to neural systems that are evolutionarily relevant for survival and balance.

The search for a homeostatic hypothesis corroborates other addiction theories that also focus on the search for regulation (10, 16, 20). Both clinical practice and scientific evidence suggest that negative affect states predispose to substance use as a way to alleviate unpleasant emotions and bring the individual to a point of balance (14, 58, 63, 64). Actually, this point of balance is maintained for a short period of time, automatically returning to the negative valence state observed previous to drug use. According to Koob, frequent use of psychoactive substances induces several neurochemical changes derived from the tolerance associated with sustained drug use, leading to what he calls hyperkatifeia, a chronic anhedonic state related to an increased threshold for pleasant emotions (63). Other authors suggest that the negative emotional states leading to substance use are due to psychiatric comorbidities, like mood and anxiety disorders. Substance use, in this sense, would be a way of self-medication (10). Social psychiatry and psychology researchers correlate the impact of environmental factors (poverty, hunger, war) with the activation of a chronic stress state that could lead to substance use and the associated consequences (65–68). Finally, many authors point out specific elements as being the cause of addiction, although the behavior pattern can originate from different factors (69–71). In conclusion, any negative valence state can be understood as risk prediction, and drug use would be an attempt to return to balance. Repetition of the same behavior reinforces the memory of reward and the prediction of a homeostatic result, consolidating the cycle. Individual genetic and environmental features, as well as the action of each substance in the central nervous system, can influence the process. For this reason, the development of addiction can occur at different time periods for each individual.

Internalizing disorders, such as mood and anxiety disorders, are directly related to feelings of hopelessness, fear, and a state of stress. Individuals with these comorbidities are four times more likely to become addicts and are more prone to relapse (72). There is also an important association between externalizing symptoms and personality disorders, as impulsivity limits the individual’s ability to control their own behavior, and the

predominance of emotional dysregulation states leads the individual to seek addictive behavior as a relief of negative states (73).

Conversely, when risk prediction concerning possible consequences of addictive behavior increases significantly, there is a trend toward protective behavior instead of substance use. This process, mediated by prefrontal structures, may suppress the addictive cycle and promote a change towards recovery. However, risk perception, too, has different components and may be influenced by type of addictive behavior (74, 75).

4 Six main transdiagnostic dimensions of dysregulation derived from DREXI3 model

In order to facilitate the identification of mind predictions and responses (emotions, thoughts, and behaviors) related to the DREXI3 model, the authors designed a reductionist transdiagnostic radar chart illustration containing the six main dimensions of externalizing and internalizing phenomena usually found in animals with addictive behaviors (Figure 4). The model highlights the differences between internalizing and externalizing phenomena associated with each of the three modes, and their evaluation could be helpful to detect changes across these modes. The terms “internalizing” and “externalizing” were originally used to describe groups of symptoms in children and adolescents and became well accepted classifications for behavioral disorders. These concepts also have an empirical basis and are useful for both clinical practice and research. While the internalizing group comprises depressive, anxiety and somatic disorders, the externalizing group represents conditions characterized by impulsive and compulsive behaviors, including addiction (76, 77). In the DREXI3 model, addiction usually presents both internalizing and externalizing symptoms, with two hyperactivated modes (Seek and Alarm Modes) and one hypoactivated mode (Balance Mode).

Figure 4 presents the six dimensions of symptoms possibly observed in addictive disorders, which are the same found in Figure 3, namely: alterations in appetite, sleep, energy, and libido; anxiety/anger; impulsivity, mood/depression; compulsion; and cognitive impairment/ psychosis. This proposal is based on the latest classifications and theories on the subject (e.g., DSM-5-TR). Among the diagnostic criteria listed, some are directly related to the patient’s inability to control substance use. For instance, use of excessive amounts of drug, difficulty to cease use, and time spent with use would be manifestations of the compulsion dimension. Use of a substance in situations that can offer risks or when substance use has physical or psychological complications would be included in the

impulsivity dimension. Craving, induced by reward memories, would be activated by predictive mechanisms that signal the need to use the drug again as a way of reducing risks/achieving balance. Finally, abstinence symptoms would be associated with risk prediction that triggers stress responses, leading the individual to self-regulating seeking behaviors (77).

Figures 5, 6 show examples of addiction progression and increasing reward prediction, respectively, from the point of view of the DREXI3 model. Figure 6, in particular, describes a possible trajectory of chronic substance use in which reward prediction increases with the use of more intense substances or stimuli in order to activate the Seek Mode despite future impairments, precipitating delay discounting and risky behaviors.

4.1 Appetite, sleep, energy, libido

The first dimension, abbreviated as appetite, sleep, energy, libido (ASEL), accounts for neurophysiological symptoms related to acute and chronic stress even in the absence of psychiatric symptoms. The relationship between disturbed sleep and addiction or psychiatric disorders is well supported by the literature. Sleep disturbances are one of the first symptoms related to stress and can be present in several mental illnesses as well, e.g., mood and anxiety disorders, psychosis, eating disorders, personality disorders. However, reduced sleep can also predispose to the development of psychiatric symptoms (78). The connection between sleep and mental illness has been analyzed in polysomnographic studies that reported sleep alterations in most disorders (79). Some studies have used models of allostasis to evaluate circadian rhythm, an essential element of physiological balance (80). Finally, addictive behaviors have been linked with adverse sleep outcomes. For instance, gaming disorder and problematic internet use have been associated with reduced sleep duration, subjective insomnia, and poor sleep quality (81–83).

Changes in appetite are linked to other physiological aspects, including sleep. The association between ghrelin (an orexigenic hormone), appetite, sleep, and depressive symptoms has been described. Some clinical findings support the hypothesis that ghrelin levels are increased in patients with hypersomnia, as both hypersomnia and hyperphagia are present in depressive episodes with atypical characteristics according to DSM-5-TR (77, 84). Even though appetite disturbances are common in different psychiatric syndromes, it is difficult to establish a causal relationship between them. Changes in diet can affect mood,

while mental illness can impact eating habits. In addition, some common factors, such as genetic predisposition, stress, and other environmental cues, can lead to both appetite modifications and mental disorders (85). When it comes to appetite and addiction, there is increasing evidence supporting a common basis for obesity and some substance use disorders (86). Appetite-regulatory peptides, such as ghrelin and leptin, can play a role in addiction development and are expected to be useful in future treatment perspectives (87–89).

Energy alterations can also be present in different psychiatric disorders, including addictions. The most typical example is the use of stimulant substances leading to increased energy, euphoria and other symptoms through adrenergic activation (90). The same is true for libido, which can be affected by acute and chronic use of psychotropic drugs. Moreover, there is a discussion about how to classify compulsive sexual behavior, as it shares some features with other addictive behaviors (91). However, as these neurophysiological symptoms can be present in distinct disorders, their association with addiction may be more complex to analyze.

4.2 Impulsivity

Impulsivity is a core feature of addictive disorders, and therefore it comprises the second dimension in this proposed framework. It has been studied as a risk factor for the development and maintenance of these disorders (92, 93) and is a characteristic of the psychopathology of some addictive behaviors (94). The instrument most widely used to analyze this feature is the Barratt Impulsiveness Scale (BIS-11), which separately assesses attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness (95). Non-planning impulsiveness, characterized by behaviors more oriented to the present than to the future, is particularly related to the concept of delay discounting. Initially derived from behavioral economics, this concept shows how some individuals discount delayed reinforcers by choosing immediate reinforcers, even though the latter are less worthy (96). Literature has described delay discounting as a marker of addictive behaviors. Therefore, this individual trait could help identify individuals at risk of developing an addiction and also influence the course of the disease and its severity, not to mention treatment choices (97, 98).

4.3 Compulsion

As discussed above, impulsivity can be considered an externalizing dimension associated or not with craving, which is an internalizing phenomenon. The same happens with compulsivity, which can also be triggered by craving – another core feature of addiction (99, 100). Compulsion, as the other dimensions of the model, is a transdiagnostic concept that can be observed in other syndromes, such as obsessive-compulsive disorder – researchers have studied brain structural changes present both in substance use disorders and obsessive-compulsive disorder (101). In the field of addiction, studies have started to focus on how compulsivity manifests across different types of addictive behaviors. A systematic meta-review has highlighted the importance of compulsivity-related neurocognition across alcohol use disorder and gambling. Nevertheless, there is a trend in those studies to understand compulsive behaviors not only as a consequence of chronic drug exposure, but as a relevant construct for addiction development (102). Another controversial topic in research is how precisely compulsivity can be defined, since it is expressed in distinct disorders. A recent systematic review highlights the need to refine compulsivity scales to achieve a more accurate analysis of these symptoms (103).

4.4 Anxiety and anger

Anxiety and anger symptoms have been included in a separate dimension. Typically, anxiety disorders have been associated with internalizing phenomena and externalizing responses, such as fight or flight (76), and personality traits, such as neuroticism. The association between social anxiety and substance use has been demonstrated. Social anxiety was positively related to alcohol problems in a meta-analysis that focused on college students (104). In alcohol use disorders, anxiety has been studied as part of a negative affect state during abstinence that increases the risk of relapse. A systematic review including animal and human studies identified a role played by the anterior insula in the abstinence network. In humans, the anterior insula is connected to the amygdala (known to be associated with anxiety and addiction) and to the nucleus accumbens (a known component of the abstinence network) (105). For instance, evidence supports a high prevalence of comorbid cannabis use and anxiety disorders, but more research is needed to establish a causal relationship between these conditions (106, 107).

In this framework, anger symptoms were placed in the same dimension as anxiety since they are usually correlated in clinical practice. However, anger and irritability can be present in other mental health conditions and personality disorders. A recent meta-analysis showed

higher rates of anger scores among psychoactive substance users when compared to non-users (108). This finding highlights the relevance of anger in the evaluation and treatment of addiction.

4.5 Mood/depression

As predictions become worse, animals in general tend to present behavioral shutdown or hopelessness responses, and mammals in particular show signs of depression. Therefore, alterations related to mood, e.g., depressive and manic symptoms, were grouped in a different dimension in this proposed framework. The comorbidity of addiction and mood disorders has been extensively investigated. A review that analyzed the association between alcohol use disorder and major depression confirmed the high prevalence of comorbidity when one of the disorders is already present. Even though that study suggests a causal relationship in which alcohol use disorder increases the risk of depression, more research is needed to define the precise mechanism of the association (109). The interaction between depression and smoking has also been widely studied. Smokers with comorbid depression are less likely to quit when compared to non-depressive smokers. A systematic review that analyzed the mechanisms behind these lower cessation rates indicated low positive affect, high negative affect, and cognitive impairment as important underlying factors. These findings corroborate the need for treatment strategies focusing on negative internal states (110). Other psychoactive substances have been associated with depression. The use of cannabis during adolescence has been linked to a higher risk of developing depression in young adulthood (111).

4.6 Consciousness, attention, sensoperception, orientation, memory, intelligence and speech

The last dimension comprises changes in consciousness, attention, sensoperception, orientation, memory, intelligence, and speech, commonly associated with acute drug abuse and chronic or severe addiction. Both intoxication with and withdrawal from some substances can cause alterations in consciousness, orientation, and attention, e.g., delirium tremens (112). Psychotic symptoms, in turn, seem to be associated with severity of the substance use disorder and the pharmacological drug profile. Literature has focused on the acute use of cannabis, cocaine, and methamphetamines as a cause of psychotic episodes. Nevertheless, more studies are necessary to evaluate the role played by other substances,

e.g., synthetic drugs, in this scenario (113). Acute cannabis use can also affect cognitive functions, including learning, memory, attention, and language; further studies should analyze the neuropsychological impact of chronic use. There is also concern about the risk of cannabis users developing psychotic episodes and even schizophrenia. Although multiple elements are known to be involved in the etiology of these disorders, cannabis use can be considered a risk factor for psychosis (114).

5 Discussion

The DREXI3 model described in this paper proposes an integrative, dynamic, transdiagnostic model for the development and maintenance of addiction. By focusing on the three homeostatic modes of the mind as a central aspect in the pathophysiology of these conditions, the authors aim to explain the process of addictive behaviors drawing on previous research into the role of emotional and behavioral regulation in these disorders (115). The present model proposes that a new paradigm of addiction, based on three modes of the mind, would allow patients to have a better understanding of the basic emotions and behaviors implicated in this complex condition, and could be useful for clinical evaluation and treatment planning.

The neurobiological basis of addiction, especially the reward system, has been widely investigated in recent years (37, 69, 99). However, evidence showing the influence of environmental factors and stress on addiction has led to the development of new frameworks (116). Some theories have focused on specific constructs, like attachment, to explain why some individuals are more prone to addiction (117). Other models argue that the emphasis on the disease model has diverted attention from other factors associated with drug use, and support that the development of addictive behaviors is a way of learning and responding to the environmental context, which may include traumas. The authors suggest that learning models may enable changes in therapeutic interventions, as the patient takes a more active role in the treatment (29).

It is clear that addiction comprises a complex group of disorders and results from multiple factors, including environmental contingencies that interact with individual neurobiological features. For instance, the role of stress in addiction has been well-documented: it can predispose to drug use via the action of stress hormones, such as the corticotropin-releasing hormone, which activates the amygdala and reduces activation of the hippocampus and

prefrontal cortex, weakening executive control and increasing negative emotions (64). Environmental conditions, including stressful events, can influence the epigenetic response to drug use and predispose to the development of a disorder (70). It has been proposed that stress related to early life adversity can increase vulnerability to addictive behaviors by causing emotional and cognitive dysregulation (116). Moreover, a history of early life adversity, such as childhood neglect, may be related to symptom severity in addictive disorders (118). Overall, there is growing research correlating stress and emotional regulation with the neurobiological alterations that contribute to the process of addiction. Addictive disorders are connected to the present framework because some of the main features of these disorders are the seeking behavior and the negative emotions that can be present in withdrawal and contribute to perpetuating the addiction cycle. According to the model, patients with substance use disorders present hyperactivation of the Seek Mode that leads them to present high levels of impulsivity and compulsivity in order to obtain reward. Impulsivity and compulsivity have been studied across different types of addiction. Some substances, like alcohol, are directly associated with brain damage and executive dysfunction, which worsen self-control toward future rewards (119). Nevertheless, studies have suggested that impulsivity is not only a consequence of chronic drug use, but may in fact, in many cases, underpin the development of substance and behavioral addiction (102). Conversely, an individual in Alarm Mode may present symptoms typically associated with depression and anxiety, which can be triggered by environmental factors in the present or the past, or even by drug withdrawal.

The evaluation and management of these symptoms, using various therapeutic interventions and approaches, could help prevent the occurrence of dysfunctional behaviors aimed at reestablishing the Balance Mode, probably reducing the chance of relapse, unless the mind predicts new risks or rewards related to the addiction behavior. For example, individuals who typically enter the Alarm Mode may benefit from interventions focused on symptoms like depression, anxiety, and irritability. Cognitive-behavioral interventions may be useful for the management of depressive and anxious symptoms (120, 121). Specific interventions, such as anger management and mindfulness-based cognitive-behavioral therapy, may be used to reduce anger and irritability (122), and there are specific interventions directed to the Seek Mode, targeting impulsivity and compulsive behaviors. Cue-exposure therapy can be considered an example of neuropsychological rehabilitation and has shown effect in reducing relapse (123). Mindfulness and other third-wave therapies have been seen as options to treat substance use disorders by acting on feelings related to craving (124, 125);

contingency management may be a way of addressing the compulsivity component (37); mindfulness-based interventions may also be used in individuals in Balance Mode to enhance well-being and improve behavioral regulation (126). Overall, the treatment based on these three modes and their dynamic involves understanding individual functioning and values that shape predictions, and not only the symptoms of addiction.

As addiction represents a heterogeneous condition, a model based on different dimensions would enable therapists to perform a more personalized assessment. The dimensions proposed by the authors represent the main psychiatric syndromes already described in categorical systems (77) and include the core features of addictive behaviors (15, 102, 127). Notwithstanding, the authors acknowledge the need to develop adequate instruments to evaluate and quantify symptoms in each dimension. At present, one of the most widely used instruments to evaluate addiction is the Addiction Severity Index-6 (ASI-6), first developed in 1980 and now in its sixth version (128, 129). In addition to evaluating the severity of addictive disorders, new instruments should analyze their relationship with emotional and behavioral dysregulation.

Many theories developed to explain addiction have focused on the common features underlying different types of addictive disorders. Substance use disorders and behavioral addictions have similarities, but the manifestations of each illness differ (130). Considering these hypotheses of underlying factors contributing to different addictive behaviors, it has been proposed that the treatment of addiction should be transdiagnostic (37). In the present framework, the authors acknowledge that some interventions may be applied to a wide range of symptoms, while others may have to be customized according to individual needs. Furthermore, recent papers citing the self-medication hypothesis suggest that homeostatic theories may play a role in the addiction field (131–133). These theories tend to be more integrative, comprising different factors that may lead to the development of addiction and potentially contributing to the development of therapeutic interventions in the future. According to Feingold and Tzur Bitan, addiction psychotherapy should have an integrative approach, addressing both psychological and social aspects (134).

Disagreements about how to conceptualize substance abuse have been present in the literature for many years (135). Despite the continuous development of addiction theories and neurobiological research, some gaps remain when applying this knowledge to clinical practice. The perspective that new therapeutic strategies will derive from neuroscience discoveries draws from the concept of addiction as a brain disease. Notwithstanding, there is a trend of considering different theories when trying to understand addiction, so it seems

unlikely that a single theory could explain the varying manifestations of this disorder. A more integrative framework may contribute towards a new understanding of addiction while raising new questions that are essential for the development of the field (33).

Considering addiction beyond its neurobiological basis may allow patients to take on new roles in therapeutic approaches. Individuals with an addiction may show biases in their choices, prioritizing maladaptive regulation rewards. However, they can still be sensitive to reward contingencies. Therefore, research into addictive disorders should consider therapeutic strategies involving more adaptive reinforcers, with patients playing a more active role in treatment (41). Furthermore, it is important to develop a model that considers the evolutive perspective of the systems that shape addictive emotions and maladaptive behaviors, in order to approach the phenomena in a dynamic way and translate findings to clinical practice and into effective public policies. Also, a model that includes evolutionary aspects could be more easily tested in animal research. The authors of this manuscript believe that the study of neurobiological aspects and systems related to the dynamic of the three modes as influenced by the environment could facilitate the validation of this addiction paradigm with animal models and its transposition to human externalizing and internalizing phenomena, in an attempt to minimize the translational crisis in the field.

McLean and Rose suggest that the compulsive, chronic, relapsing hallmarks of substance addiction can be explained through neurochemical maladaptations, and that these behaviors are in part the result of associations established with rewarding cues present in the environment. Such associations, combined with meanings given to experiences, could be represented in drug memories and memory systems, which those authors refer to as “neuro social relations.” They defend that a possible way of addressing the translational crisis would be by improving the understanding of these relations (136). The DREXI3 model accounts for these aspects by valuing the role of memory and its interaction with the environment to evaluate risk and reward. Furthermore, a transdiagnostic treatment approach to addictive disorders could have several benefits compared to the most common therapeutic strategies by focusing on the regulation of specific symptoms rather than on stopping drugs or other stimuli.

In conclusion, the conceptualization of addictive behaviors in association with cognitive and emotional responses that influence choices in a dynamic process involving modes and systems of the mind highlights the importance of cognitive function and decision-making over a narrow focus on the classical reward circuitry. The DREXI3 model described in this paper was developed using an integrative approach to the understanding of addiction, mainly

based on a homeostatic purpose of the mind and aiming to be less stigmatizing and to improve the range of effective approaches based on the best scientific evidence to these behavioral disorders. According to this framework, addiction treatment should also be integrative and tailored to the needs of each individual. Previous research supports the influence of stress, emotional regulation, and environmental factors in addictive disorders. In the present framework, that knowledge is integrated with the hypothesis that the mind can work in three different modes, according to levels of stress and risk prediction.

Finally, the DREXI3 model proposed in this manuscript represents an innovative and potentially transformative framework for addiction understanding and treatment. By prioritizing cognitive function and decision-making processes and emphasizing the role of emotional, learning feedback and stress-related responses, this model offers a comprehensive lens through which addiction can be viewed. It is supposed to be a shift from the conventional focus on reward circuitry. The holistic approach it embodies looks for a reduction in stigma and an increase in effective, personalized treatment approaches. For the scientific community, this model could serve as a platform for future research, especially in exploring new treatment strategies that are tailored to individual needs. The understanding of addiction as a heterogeneous condition that can present with varying symptoms may foster the development of new treatment strategies in future research. Clinicians stand to benefit from the model's integrative approach, potentially enhancing the therapeutic outcomes for patients. Moreover, patients themselves could gain a deeper insight into the nature of their condition, leading to more informed choices and better management of their own treatment paths. However, authors will encourage continued debate about possible limitations of this theoretical framework which needs to be explored and refined in order to substantiate its further applications. Considering the constant evolution of science, these possible limitations may be revised and integrated in the future. Additionally, a deeper understanding of addictive disorders could reduce stigma and contribute to more effective public policies concerning drugs.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

BL: Conceptualization, Writing – original draft, Writing – review & editing. AS: Conceptualization, Writing – original draft, Writing – review & editing. MeC: Writing – review & editing. FO: Writing – review & editing. EGu: Writing – original draft, Writing – review & editing. TR: Writing – original draft, Writing – review & editing. JS: Writing – review & editing. MaC: Writing – review & editing. FP: Writing – review & editing. EGr: Writing – review & editing. RG-O: Writing – original draft, Writing – review & editing. LD: Writing – review & editing. FK: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Labor Unooda. *World Drug Report 2021 (Set of 5 Booklets)*. SL: United Nations (2022).

2. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. (2018) 392:1736–88. doi: 10.1016/S0140-6736(18)32203-7

3. Rehm J, Shield KD. Global burden of disease and the impact of mental and addictive disorders. *Curr Psychiatry Rep*. (2019) 21:10. doi: 10.1007/s11920-019-0997-0

4. Amato L, Davoli M, Ferri M, Gowing L, Perucci CA. Effectiveness of interventions on opiate withdrawal treatment: an overview of systematic reviews. *Drug Alcohol Depend*. (2004) 73:219–26. doi: 10.1016/j.drugalcdep.2003.11.002

5. Carmen B, Angeles M, Ana M, María AJ. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction*. (2004) 99:811–28. doi: 10.1111/j.1360-0443.2004.00763.x

6. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Rev*. (2014) 2014:CD000031. doi: 10.1002/14651858. CD000031.pub4

7. Volkow ND, Fowler JS, Wang GJ. Role of dopamine in drug reinforcement and addiction in humans: results from imaging studies. *Behav Pharmacol*. (2002) 13:355–66. doi: 10.1097/00008877-200209000-00008

8. Field M, Cox W. Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug Alcohol Depend*. (2008) 97:1–20. doi: 10.1016/j. drugalcdep.2008.03.030

9. Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta-analysis of voucher-based reinforcement therapy for substance use disorders. *Addiction*. (2006) 101:192–203. doi: 10.1111/j.1360-0443.2006.01311.x

10. Khantzian J. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry*. (1985) 142:1259–64. doi: 10.1176/ ajp.142.11.1259

11. Khantzian EJ. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harv Rev Psychiatry*. (1997) 4:231–44. doi: 10.3109/10673229709030550

12. Ahmed SH. Validation crisis in animal models of drug addiction: beyond non-disordered drug use toward drug addiction. *Neurosci Biobehav Rev*. (2010) 35:172–84. doi: 10.1016/j.neubiorev.2010.04.005

13. Kandel DB, Andrews K. Processes of adolescent socialization by parents and peers. *Int J Addict*. (1987) 22:319–42. doi: 10.3109/10826088709027433

14. Koob GF. Hedonic homeostatic dysregulation as a driver of drug-seeking behavior. *Drug Discov Today Dis Models*. (2008) 5:207–15. doi: 10.1016/j.ddmod.2009.04.002

15. Perry JL, Carroll ME. The role of impulsive behavior in drug abuse. *Psychopharmacology*. (2008) 200:1–26. doi: 10.1007/s00213-008-1173-0

16. Koob GF, Sanna PP, Bloom FE. Neuroscience of addiction. *Neuron*. (1998) 21:467–76. doi: 10.1016/S0896-6273(00)80557-7

17. Blaszczynski A, Nower L. A pathways model of problem and pathological gambling: pathways model of gambling. *Addiction*. (2002) 97:487–99. doi: 10.1046/j.1360-0443.2002.00015.x

18. Hussong AM, Jones DJ, Stein GL, Baucom DH, Boeding S. An internalizing pathway to alcohol use and disorder. *Psychol Addict Behav*. (2011) 25:390–404. doi: 10.1037/a0024519

19. Muraven M, Baumeister RF. Self-regulation and depletion of limited resources: does self-control resemble a muscle? *Psychol Bull*. (2000) 126:247–59. doi: 10.1037/0033-2909.126.2.247

20. European Monitoring Centre for Drugs and Drug Addiction. *Models of Addiction*. LU: Publications Office (2013).

21. Christakis NA, Fowler JH. The collective dynamics of smoking in a large social network. *N Engl J Med*. (2008) 358:2249–58. doi: 10.1056/NEJMsa0706154

22. Rosenquist JN. The spread of alcohol consumption behavior in a large social network. *Ann Intern Med*. (2010) 152:426–33, W141. doi: 10.7326/0003-4819-152-7-201004060-00007

23. Ornstein SI. Control of alcohol consumption through price increase. *J Stud Alcohol*. (1980) 41:807–18. doi: 10.15288/jsa.1980.41.807

24. Pekurinen M, Valtonen H. Price, policy and consumption of tobacco: the Finnish experience. *Soc Sci Med*. (1987) 25:875–81. doi: 10.1016/0277-9536(87)90256-5

25. DeJONG W, Schneider SK, Towvim LG, Murphy MJ, Doerr EE, Simonsen NR, et al. A multisite Randomized trial of social norms marketing campaigns to reduce college student drinking. *J Stud Alcohol*. (2006) 67:868–79. doi: 10.15288/jsa.2006.67.868

26. Gordon R, MacKintosh AM, Moodie C. The impact of alcohol marketing on youth drinking behaviour: a two-stage cohort study. *Alcohol Alcohol*. (2010) 45:470–80. doi: 10.1093/alcalc/agq047

27. Ahn AC, Tewari M, Poon CS, Phillips RS. The clinical applications of a systems approach. *PLoS Med*. (2006) 3:e209. doi: 10.1371/journal.pmed.0030209

28. Chambers RA, Bickel WK, Potenza MN. A scale-free systems theory of motivation and addiction. *Neurosci Biobehav Rev*. (2007) 31:1017–45. doi: 10.1016/j. neubiorev.2007.04.005

29. Lewis M. Brain change in addiction as learning, not disease. *N Engl J Med*. (2018) 379:1551–60. doi: 10.1056/NEJMra1602872

30. Stein DJ, Szatmari P, Gaebel W, Berk M, Vieta E, Maj M, et al. Mental, behavioral and neurodevelopmental disorders in the ICD-11: an international perspective on key changes and controversies. *BMC Med*. (2020) 18:21. doi: 10.1186/s12916-020-1495-2

31. Gaebel W, Stricker J, Kerst A. Changes from ICD-10 to ICD-11 and future directions in psychiatric classification. *Dialogues Clin Neurosci*. (2020) 22:7–15. doi: 10.31887/DCNS.2020.22.1/wgaebel

32. Hengartner MP, Lehmann SN. Why psychiatric research must abandon traditional diagnostic classification and adopt a fully dimensional scope: two solutions to a persistent problem. *Front Psych*. (2017) 8:101. doi: 10.3389/fpsyt.2017.00101

33. Bickel WK, Crabbe JC, Sher KJ. What is addiction? How can animal and human research be used to advance research, diagnosis, and treatment of alcohol and other substance use disorders? *Alcohol Clin Exp Res*. (2019) 43:6–21. doi: 10.1111/acer.13912

34. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. (2010) 167:748–51. doi: 10.1176/appi.ajp.2010.09091379

35. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, et al. The hierarchical taxonomy of psychopathology (HiTOP): a dimensional alternative to traditional nosologies. *J Abnorm Psychol*. (2017) 126:454–77. doi: 10.1037/abn0000258

36. Michelini G, Palumbo IM, DeYoung CG, Latzman RD, Kotov R. Linking RDoC and HiTOP: a new interface for advancing psychiatric nosology and neuroscience. *Clin Psychol Rev*. (2021) 86:102025. doi: 10.1016/j.cpr.2021.102025

37. Kim HS, Hodgins DC. Component model of addiction treatment: a pragmatic transdiagnostic treatment model of behavioral and substance addictions. *Front Psych*. (2018) 9:406. doi: 10.3389/fpsyt.2018.00406

38. Robison AJ, Nestler EJ. Transcriptional and epigenetic mechanisms of addiction. *Nat Rev Neurosci*. (2011) 12:623–37. doi: 10.1038/nrn3111

39. Piazza PV, Deroche-Gamonet V. A multistep general theory of transition to addiction. *Psychopharmacology*. (2013) 229:387–413. doi: 10.1007/s00213-013-3224-4

40. Brady JV. Animal models for assessing drugs of abuse. *Neurosci Behav Rev*. (1991) 15:35–43. doi: 10.1016/S0149-7634(05)80089-2

41. Heilig M, Augier E, Pfarr S, Sommer WH. Developing neuroscience-based treatments for alcohol addiction: a matter of choice? *Transl Psychiatry*. (2019) 9:255. doi: 10.1038/s41398-019-0591-6

42. Billman GE. Homeostasis: the underappreciated and far too often ignored central organizing principle of physiology. *Front Physiol*. (2020) 11:200. doi: 10.3389/ fphys.2020.00200

43. Cannon WB. *The Wisdom of the Body*. WW Norton & Co. (1932).

44. Cooper SJ. From claude bernard to walter cannon. Emergence of the concept of homeostasis. *Appetite*. (2008) 51:419–27. doi: 10.1016/j.appet.2008.06.005

45. Rosenblueth A, Wiener N, Bigelow J. Behavior, purpose and teleology. *Philos Sci*. (1943) 10:18–24. doi: 10.1086/286788

46. Yon D, Heyes C, Press C. Beliefs and desires in the predictive brain. *Nat Commun*. (2020) 11:4404. doi: 10.1038/s41467-020-18332-9

47. Nave K, Deane G, Miller M, Clark A. Wilding the predictive brain. *WIREs Cogn Sci*. (2020) 11:e1542. doi: 10.1002/wcs.1542

48. Noble D. Evolution viewed from physics, physiology and medicine. *Interface Focus*. (2017) 7:20160159. doi: 10.1098/rsfs.2016.0159

49. Damasio A, Carvalho GB. The nature of feelings: evolutionary and neurobiological origins. *Nat Rev Neurosci*. (2013) 14:143–52. doi: 10.1038/nrn3403

50. Gilbert P. Evolution and depression: issues and implications. *Psychol Med*. (2006) 36:287–97. doi: 10.1017/S0033291705006112

51. Roelofs K, Dayan P. Freezing revisited: coordinated autonomic and central optimization of threat coping. *Nat Rev Neurosci*. (2022) 23:568–80. doi: 10.1038/ s41583-022-00608-2

52. Wright JS, Panksepp J. An evolutionary framework to understand foraging, wanting, and desire: the neuropsychology of the SEEKING system. *Neuropsychoanalysis*. (2012) 14:5–39. doi: 10.1080/15294145.2012.10773683

53. Alexander AC, Waring JJC, Olurotimi O, Kurien J, Noble B, Businelle MS, et al. The relations between discrimination, stressful life events, and substance use among adults experiencing homelessness. *Stress Health*. (2022) 38:79–89. doi: 10.1002/smi.3073

54. Depue RA, Morrone-Strupinsky JV. A neurobehavioral model of affiliative bonding: implications for conceptualizing a human trait of affiliation. *Behav. Brain Sci.* (2005) 28:313–50. doi: 10.1017/S0140525X05000063

55. Porges SW. The polyvagal perspective. *Biol Psychol*. (2007) 74:116–43. doi: 10.1016/j.biopsycho.2006.06.009

56. Alexander R, Aragón OR, Bookwala J, Cherbuin N, Gatt JM, Kahrilas IJ, et al. The neuroscience of positive emotions and affect: implications for cultivating happiness and wellbeing. *Neurosci Biobehav Rev*. (2021) 121:220–49. doi: 10.1016/j.neubiorev.2020.12.002

57. Smallwood J, Bernhardt BC, Leech R, Bzdok D, Jefferies E, Margulies DS. The default mode network in cognition: a topographical perspective. *Nat Rev Neurosci*. (2021) 22:503–13. doi: 10.1038/s41583-021-00474-4

58. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. (2016) 3:760–73. doi: 10.1016/S2215-0366(16)00104-8

59. Jacobs DF. A general theory of addictions: a new theoretical model. *J Gambl Behav*. (1986) 2:15–31. doi: 10.1007/BF01019931

60. Karnib N, van Staaden MJ. The deep roots of addiction: a comparative perspective. *Brain Behav Evol*. (2020) 95:222–9. doi: 10.1159/000514180

61. Ervin FR, Palmour RM, Young SN, Guzman-Flores C, Juarez J. Voluntary consumption of beverage alcohol by vervet monkeys: population screening, descriptive behavior and biochemical measures. *Pharmacol Biochem Behav*. (1990) 36:367–73. doi: 10.1016/0091-3057(90)90417-G

62. Durrant R, Adamson S, Todd F, Sellman D. Drug use and addiction: evolutionary perspective. *Aust N Z J Psychiatry*. (2009) 43:1049–56. doi: 10.3109/00048670903270449

63. Koob GF. Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development. *Pharmacol Rev*. (2021) 73:163–201. doi: 10.1124/pharmrev.120.000083

64. Ruisoto P, Contador I. The role of stress in drug addiction. An integrative review. *Physiol Behav*. (2019) 202:62–8. doi: 10.1016/j.physbeh.2019.01.022

65. Collins SE. Associations between socioeconomic factors and alcohol outcomes. *Alcohol Res*. (2013) 32:135–45.

66. Hiscock R, Bauld L, Amos A, Fidler JA, Munafò M, Munafò M. Socioeconomic status and smoking: a review. *Ann N Y Acad Sci*. (2012) 1248:107–23. doi: 10.1111/j.1749-6632.2011.06202.x

67. Cheng HG, Shidhaye R, Charlson F, Deng F, Lyngdoh T, Chen S, et al. Social correlates of mental, neurological, and substance use disorders in China and India: a review. *Lancet Psychiatry*. (2016) 3:882–99. doi: 10.1016/S2215-0366(16)30166-3

68. Kelsall HL, Wijesinghe MSD, Creamer MC, McKenzie DP, Forbes AB, Page MJ, et al. Alcohol use and substance use disorders in gulf war, Afghanistan, and Iraq war veterans compared with nondeployed military personnel. *Epidemiol Rev*. (2015) 37:38–54. doi: 10.1093/epirev/mxu014

69. Volkow ND, Michaelides M, Baler R. The neuroscience of drug reward and addiction. *Physiol Rev*. (2019) 99:2115–40. doi: 10.1152/physrev.00014.2018

70. Cadet JL. Epigenetics of stress, addiction, and resilience: therapeutic implications. *Mol Neurobiol*. (2016) 53:545–60. doi: 10.1007/s12035-014-9040-y

71. Mohammadnezhad M, Thomas A, Kabir R. Determinants and prevention strategies of substance abuse in Pacific countries: a systematic review. *Oman Med J*. (2020) 35:e187–7. doi: 10.5001/omj.2020.128

72. Castillo-Carniglia A, Keyes KM, Hasin DS, Cerdá M. Psychiatric comorbidities in alcohol use disorder. *Lancet Psychiatry*. (2019) 6:1068–80. doi: 10.1016/S2215-0366(19) 30222-6

73. Farmer RF, Gau JM, Seeley JR, Kosty DB, Sher KJ, Lewinsohn PM. Internalizing and externalizing disorders as predictors of alcohol use disorder onset during three developmental periods. *Drug Alcohol Depend*. (2016) 164:38–46. doi: 10.1016/j. drugalcdep.2016.04.021

74. Bujalski M, Wieczorek Ł, Sierosławski J. Risk perception and risk aversion among people who use new psychoactive substances. *Int J Drug Policy*. (2021) 97:103326. doi: 10.1016/j.drugpo.2021.103326

75. Ferrer RA, Klein WMP, Avishai A, Jones K, Villegas M, Sheeran P. When does risk perception predict protection motivation for health threats? A person-by-situation analysis. *PLoS One*. (2018) 13:e0191994. doi: 10.1371/journal.pone.0191994

76. Achenbach TM, Ivanova MY, Rescorla LA, Turner LV, Althoff RR. Internalizing/ externalizing problems: review and recommendations for clinical and research applications. *J Am Acad Child Adolesc Psychiatry*. (2016) 55:647–56. doi: 10.1016/j. jaac.2016.05.012

77. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: fifth edition text revision DSM-5-TR™*. Washington, DC: American Psychiatric Association (2022).

78. Pires GN, Bezerra AG, Tufik S, Andersen ML. Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. *Sleep Med*. (2016) 24:109–18. doi: 10.1016/j.sleep.2016.07.019

79. Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, et al. Sleep and mental disorders: a meta-analysis of polysomnographic research. *Psychol Bull*. (2016) 142:969–90. doi: 10.1037/bul0000053

80. McEwen BS, Karatsoreos IN. Sleep deprivation and circadian disruption. *Sleep Med Clin*. (2015) 10:1–10. doi: 10.1016/j.jsmc.2014.11.007

81. Alimoradi Z, Lin CY, Broström A, Bülow PH, Bajalan Z, Griffiths MD, et al. Internet addiction and sleep problems: a systematic review and meta-analysis. *Sleep Med Rev*. (2019) 47:51–61. doi: 10.1016/j.smrv.2019.06.004

82. Kristensen JH, Pallesen S, King DL, Hysing M, Erevik EK. Problematic gaming and sleep: a systematic review and meta-analysis. *Front Psych*. (2021) 12:675237. doi: 10.3389/fpsyt.2021.675237

83. Lam LT. Internet gaming addiction, problematic use of the Internet, and sleep problems: a systematic review. *Curr Psychiatry Rep*. (2014) 16:444. doi: 10.1007/s11920-014-0444-1

84. Morin V, Hozer F, Costemale-Lacoste JF. The effects of ghrelin on sleep, appetite, and memory, and its possible role in depression: a review of the literature. *L'Encéphale*. (2018) 44:256–63. doi: 10.1016/j.encep.2017.10.012

85. Bremner J, Moazzami K, Wittbrodt M, Nye J, Lima B, Gillespie C, et al. Diet, stress and mental health. *Nutrients*. (2020) 12:2428. doi: 10.3390/nu12082428

86. Thorgeirsson TE, Gudbjartsson DF, Sulem P, Besenbacher S, Styrkarsdottir U, Thorleifsson G, et al. A common biological basis of obesity and nicotine addiction. *Transl Psychiatry*. (2013) 3:e308–8. doi: 10.1038/tp.2013.81

87. Bach P, Koopmann A, Kiefer F. The impact of appetite-regulating neuropeptide leptin on alcohol use, alcohol craving and addictive behavior: a systematic review of preclinical and clinical data. *Alcohol Alcohol*. (2021) 56:149–65. doi: 10.1093/alcalc/agaa044

88. Shevchouk OT, Tufvesson-Alm M, Jerlhag E. An overview of appetite-regulatory peptides in addiction processes; from bench to bed side. *Front Neurosci*. (2021) 15:774050. doi: 10.3389/fnins.2021.774050

89. Koopmann A, Schuster R, Kiefer F. The impact of the appetite-regulating, orexigenic peptide ghrelin on alcohol use disorders: a systematic review of preclinical and clinical data. *Biol Psychol*. (2018) 131:14–30. doi: 10.1016/j.biopsycho.2016.12.012

90. Park TM, Haning WF. Stimulant use disorders. *Child Adolesc Psychiatr Clin N Am*. (2016) 25:461–71. doi: 10.1016/j.chc.2016.02.004

91. Kraus L, Augustin R, Kunz-Ebrecht S, Orth B. Drug use patterns and drug-related disorders of cocaine users in a sample of the general population in Germany. *Eur Addict Res*. (2007) 13:116–25. doi: 10.1159/000097942

92. Leung D, Staiger PK, Hayden M, Lum JAG, Hall K, Manning V, et al. Meta-analysis of the relationship between impulsivity and substance-related cognitive biases. *Drug Alcohol Depend*. (2017) 172:21–33. doi: 10.1016/j.drugalcdep.2016.11.034

93. Nawi AM, Ismail R, Ibrahim F, Hassan MR, Manaf MRA, Amit N, et al. Risk and protective factors of drug abuse among adolescents: a systematic review. *BMC Public Health*. (2021) 21:2088. doi: 10.1186/s12889-021-11906-2

94. Chowdhury NS, Livesey EJ, Blaszczynski A, Harris JA. Pathological gambling and motor impulsivity: a systematic review with meta-analysis. *J Gambl Stud*. (2017) 33:1213–39. doi: 10.1007/s10899-017-9683-5

95. Patton JH, Stanford MS, Barratt ES. Factor structure of the barratt impulsiveness scale. *J Clin Psychol*. (1995) 51:768–74. doi: 10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1

96. Bickel WK, Marsch LA. Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction*. (2001) 96:73–86. doi: 10.1046/ j.1360-0443.2001.961736.x

97. Bickel WK, Jarmolowicz DP, Mueller ET, Koffarnus MN, Gatchalian KM. Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: emerging evidence. *Pharmacol Ther*. (2012) 134:287–97. doi: 10.1016/j.pharmthera.2012.02.004

98. Bickel WK, Koffarnus MN, Moody L, Wilson AG. The behavioral- and neuro-economic process of temporal discounting: a candidate behavioral marker of addiction. *Neuropharmacology*. (2014) 76:518–27. doi: 10.1016/j.neuropharm.2013.06.013

99. Volkow ND. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex*. (2000) 10:318–25. doi: 10.1093/cercor/10.3.318

100. Kramer J, Dick DM, King A, Ray LA, Sher KJ, Vena A, et al. Mechanisms of alcohol addiction: bridging human and animal studies. *Alcohol Alcohol*. (2020) 55:603–7. doi: 10.1093/alcalc/agaa068

101. Klugah-Brown B, Jiang C, Agoalikum E, Zhou X, Zou L, Yu Q, et al. Common abnormality of gray matter integrity in substance use disorder and obsessive-compulsive disorder: a comparative voxel-based meta-analysis. *Hum Brain Mapp*. (2021) 42:3871–86. doi: 10.1002/hbm.25471

102. Lee RSC, Hoppenbrouwers S, Franken I. A systematic Meta-review of impulsivity and compulsivity in addictive behaviors. *Neuropsychol Rev*. (2019) 29:14–26. doi: 10.1007/s11065-019-09402-x

103. Muela I, Navas JF, Ventura-Lucena JM, Perales JC. How to pin a compulsive behavior down: a systematic review and conceptual synthesis of compulsivity-sensitive items in measures of behavioral addiction. *Addict Behav*. (2022) 134:107410. doi: 10.1016/j.addbeh.2022.107410

104. Schry AR, White SW. Understanding the relationship between social anxiety and alcohol use in college students: a meta-analysis. *Addict Behav*. (2013) 38:2690–706. doi: 10.1016/j.addbeh.2013.06.014

105. Flook EA, Luchsinger JR, Silveri MM, Winder DG, Benningfield MM, Blackford JU. Anxiety during abstinence from alcohol: a systematic review of rodent and human evidence for the anterior insula's role in the abstinence network. *Addict Biol*. (2021) 26:e12861. doi: 10.1111/adb.12861

106. Crippa JA, Zuardi AW, Martín-Santos R, Bhattacharyya S, Atakan Z, McGuire P, et al. Cannabis and anxiety: a critical review of the evidence. *Hum Psychopharmacol Clin Exp*. (2009) 24:515–23. doi: 10.1002/hup.1048

107. Onaemo VNFawehinmi TO, D'Arcy C. Comorbid Cannabis use disorder with major depression and generalized anxiety disorder: a systematic review with meta-analysis of nationally representative epidemiological surveys. *J Affect Disord*. (2021) 281:467–75. doi: 10.1016/j.jad.2020.12.043

108. Laitano HV, Ely A, Sordi AO, Schuch FB, Pechansky F, Hartmann T, et al. Anger and substance abuse: a systematic review and meta-analysis. *Braz J Psychiatry*. (2022) 44:103–10. doi: 10.1590/1516-4446-2020-1133

109. Boden JM, Fergusson DM. Alcohol and depression: alcohol and depression. *Addiction*. (2011) 106:906–14. doi: 10.1111/j.1360-0443.2010.03351.x

110. Mathew AR, Hogarth L, Leventhal AM, Cook JW, Hitsman B. Cigarette smoking and depression comorbidity: systematic review and proposed theoretical model: smoking and depression. *Addiction*. (2017) 112:401–12. doi: 10.1111/ add.13604

111. Gobbi G, Atkin T, Zytynski T, Wang S, Askari S, Boruff J, et al. Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. *JAMA Psychiatry*. (2019) 76:426. doi: 10.1001/jamapsychiatry.2018.4500

112. Mainerova B, Prasko J, Latalova K, Axmann K, Cerna M, Horacek R, et al. Alcohol withdrawal delirium - diagnosis, course and treatment. *Biomed Pap*. (2015) 159:44–52. doi: 10.5507/bp.2013.089

113. Fiorentini A, Cantù F, Crisanti C, Cereda G, Oldani L, Brambilla P. Substance-induced psychoses: an updated literature review. *Front Psych*. (2021) 12:694863. doi: 10.3389/fpsyt.2021.694863

114. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, et al. Effects of Cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA Psychiatry*. (2016) 73:292–7. doi: 10.1001/jamapsy chiatry.2015.3278

115. Weiss NH, Kiefer R, Goncharenko S, Raudales AM, Forkus SR, Schick MR, et al. Emotion regulation and substance use: a meta-analysis. *Drug Alcohol Depend*. (2022) 230:109131. doi: 10.1016/j.drugalcdep.2021.109131

116. Al'absi M. The influence of stress and early life adversity on addiction: psychobiological mechanisms of risk and resilience. *Int Rev Neurobiol*. (2020) 152:71–100. doi: 10.1016/bs.irn.2020.03.012

117. Schindler A. Attachment and substance use disorders—theoretical models, empirical evidence, and implications for treatment. *Front Psych*. (2019) 10:727. doi: 10.3389/fpsyt.2019.00727

118. Francke ID, Viola TW, Tractenberg SG, Grassi-Oliveira R. Childhood neglect and increased withdrawal and depressive severity in crack cocaine users during early abstinence. *Child Abuse Negl*. (2013) 37:883–9. doi: 10.1016/j. chiabu.2013.04.008

119. Maharjan S, Amjad Z, Abaza A, Vasavada AM, Sadhu A, Valencia C, et al. Executive dysfunction in patients with alcohol use disorder: a systematic review. *Cureus*. (2022) 14:e29207. doi: 10.7759/cureus.29207

120. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for Adult depression, alone and in comparison with other treatments. *Can J Psychiatr*. (2013) 58:376–85. doi: 10.1177/070674371305800702

121. Hofmann SG. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *J Clin Psychiatry*. (2008) 69:621–32. doi: 10.4088/jcp.v69n0415

122. Richard Y, Tazi N, Frydecka D, Hamid MS, Moustafa AA. A systematic review of neural, cognitive, and clinical studies of anger and aggression. *Curr Psychol*. (2022):1–13. doi: 10.1007/s12144-022-03143-6

123. Kiyak C, Simonetti ME, Norton S, Deluca P. The efficacy of cue exposure therapy on alcohol use disorders: a quantitative meta-analysis and systematic review. *Addict Behav*. (2023) 139:107578. doi: 10.1016/j.addbeh.2022.107578

124. Byrne SP, Haber P, Baillie A, Costa DSJ, Fogliati V, Morley K. Systematic reviews of mindfulness and acceptance and commitment therapy for alcohol use disorder: should we be using third wave therapies? *Alcohol Alcohol*. (2019) 54:159–66. doi: 10.1093/alcalc/agy089

125. Li W, Howard MO, Garland EL, McGovern P, Lazar M. Mindfulness treatment for substance misuse: a systematic review and meta-analysis. *J Subst Abus Treat*. (2017) 75:62–96. doi: 10.1016/j.jsat.2017.01.008

126. Keng SL, Smoski MJ, Robins CJ. Effects of mindfulness on psychological health: a review of empirical studies. *Clin Psychol Rev*. (2011) 31:1041–56. doi: 10.1016/j.cpr.2011.04.006

127. Morris VL, Huffman LG, Naish KR, Holshausen K, Oshri A, McKinnon M, et al. Impulsivity as a mediating factor in the association between posttraumatic stress disorder symptoms and substance use. *Psychol Trauma Theory Res Pract Policy*. (2020) 12:659–68. doi: 10.1037/tra0000588

128. McLellan T, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic evaluation instrument for substance abuse patients the addiction Seveity index. *J Nerv Ment Dis*. (1980) 168:26–33. doi: 10.1097/00005053-198001000-00006

129. Thomas McLellan A, Cacciola JC, Alterman AI, Rikoon SH, Carise D. The addiction severity index at 25: origins, contributions and transitions. *Am J Addict*. (2006) 15:113–24. doi: 10.1080/10550490500528316

130. Shaffer HJ, LaPlante DA, LaBrie RA, Kidman RC, Donato AN, Stanton MV. Toward a syndrome model of addiction: multiple expressions, common etiology. *Harv Rev Psychiatry*. (2004) 12:367–74. doi: 10.1080/10673220490905705

131. Khantzian EJ. Commentary: it is not about supply, it is about demand: why the self-medication hypotheses is still so important. *Am J Addict*. (2021) 30:301–4. doi: 10.1111/ajad.13111

132. Smith LL, Yan F, Charles M, Mohiuddin K, Tyus D, Adekeye O, et al. Exploring the link between substance use and mental health status: what can we learn from the self-medication theory? *J Health Care Poor Underserved*. (2017) 28:113–31. doi: 10.1353/hpu.2017.0056

133. Alexander AC, Ward KD. Understanding Postdisaster substance use and psychological distress using concepts from the self-medication hypothesis and social cognitive theory. *J Psychoactive Drugs*. (2018) 50:177–86. doi: 10.1080/02791072.2017.1397304

134. Feingold D, Tzur Bitan D. Addiction psychotherapy: going beyond self-medication. *Front Psych*. (2022) 13:820660. doi: 10.3389/fpsyt.2022.820660

135. Nesse RM. An evolutionary perspective on substance abuse. *Ethol Sociobiol*. (1994) 15:339–48. doi: 10.1016/0162-3095(94)90007-8

136. McLean S, Rose N. Crisis, what crisis? Addiction neuroscience and the challenges of translation. *Wellcome Open Res*. (2020) 5:215. doi: 10.12688/wellcomeopenres.16265.1

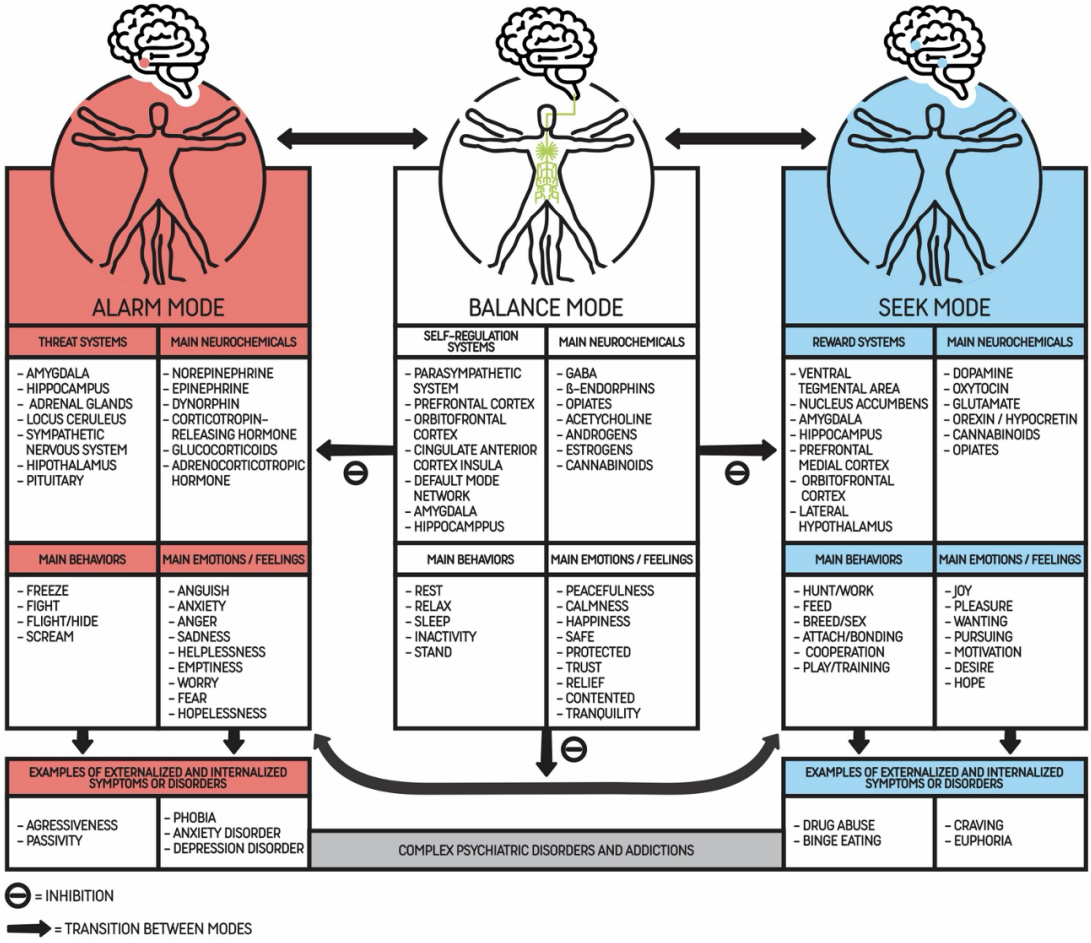


FIGURE 1

Three main modes of the predostatic mind and its main systems, behaviors, emotions and neurochemicals. This figure represents the three modes of the mind: Alarm Mode, Balance Mode, and Seek Mode. Each mode is characterized by the most known associated systems, neurochemicals, behaviors, and emotions, although some of these phenomena can be activated (inhibition or stimulation) in other modes as well. Behaviors are considered externalizing phenomena, while emotions and thoughts are associated with internalizing phenomena. Each mode is activated according to risk prediction in a dynamic way. The main usual target is to keep the organism in Balance Mode. It is relevant to highlight that culture or scarcity could push people to increase activation of the Seek Mode. The arrows indicate possible transitions between modes through stimulation and/or inhibition of systems. Worthy of note is the fact that in complex animals, such as mammals, especially *Homo sapiens*, it is common to report emotions and behaviors from different modes at the same time. When internalizing and externalizing phenomena become maladaptive or excessive from a social/cultural perspective, they can be considered symptoms that could lead to a psychiatric diagnosis of mental disorders, in particular addictions.

Figure 1.

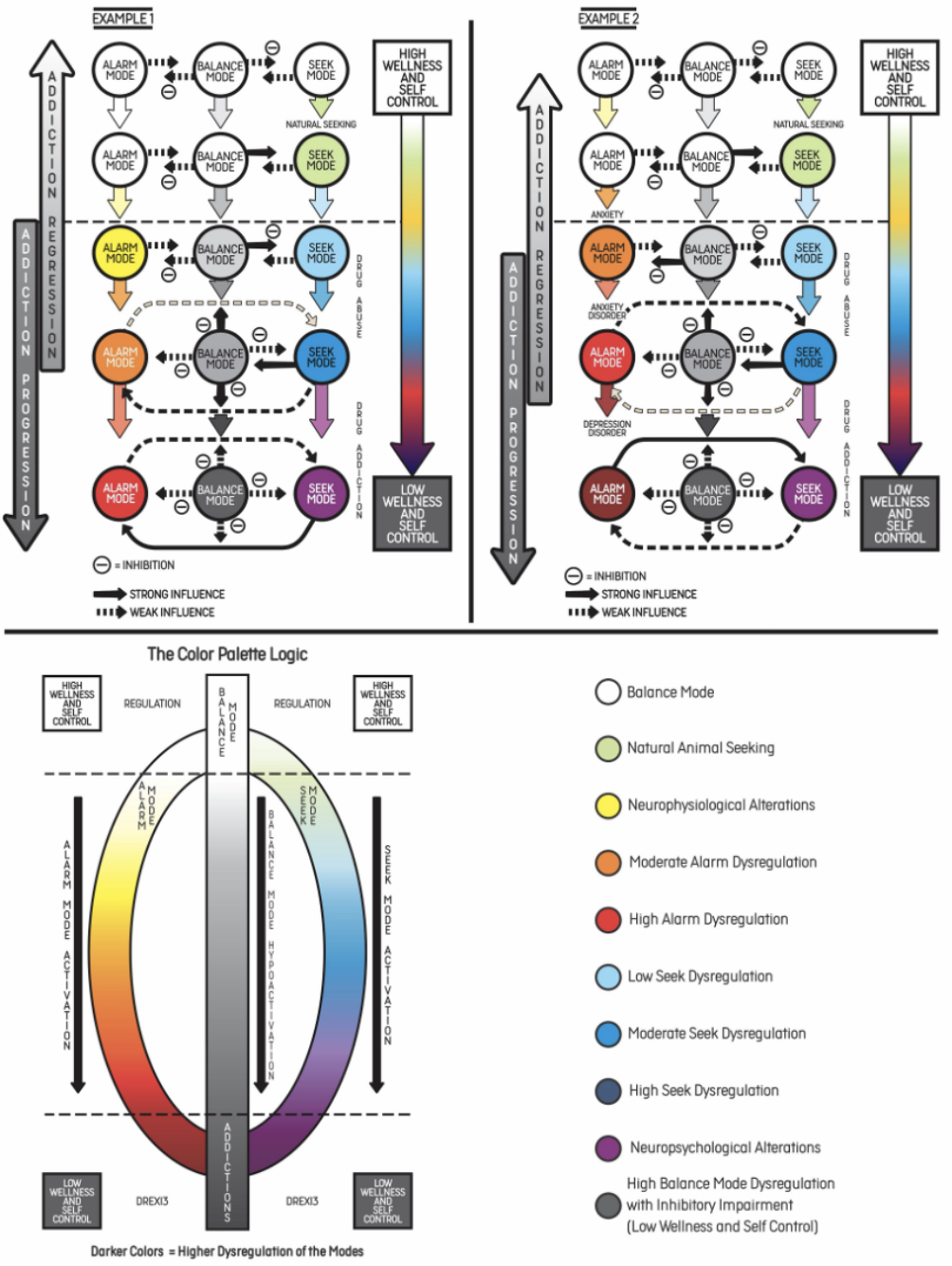


FIGURE 2

Two examples of addiction progression based on increasing dysregulation of psychobehavioral phenomena related to the three main modes of the predostatic mind. Example 1: This example illustrates the progression of addiction in young patients without psychiatric comorbidities who have been experimenting with cocaine at an increasing consumption rate over time, activating the Seek Mode and replacing natural seeking behaviors, such as sleeping, eating or having sex, with drug use. Chronic drug use can lead to withdrawal symptoms, which are related to the Alarm Mode, resulting in negative emotions or even psychiatric symptoms. According to the DREXI3 model, these patients were initially in Balance Mode, with high levels of wellness and self-control, but this chronic cycle with hyperactivation of the Seek and Alarm Modes led to addiction and long-term consequences. When a reinforcing stimulus is present (e.g., video game or the use of psychoactive substance), dysregulation of physiological functions may occur (appetite, sleep, energy, libido) as well as hyperactivation of the Seek Mode, with consequent memory and future salience of this stimulus (craving). This may lead to increased impulsivity and facilitate progression to substance abuse in individuals with a genetic predisposition. Consequently, the Alarm Mode and the Seek Mode become progressively more dysregulated, as represented by the evolution of colors. The high dysregulation of the

(Continued)

FIGURE 2 (Continued)

modes tends to sustain the addictive process, creating a coping habit in order to face inner or outer stressors. On the right side of the figure, the color palette represents the logic of hyperactivation of the Alarm and Seek Modes, or hypoactivation of the Balance Mode (from white to gray). Example 2: This example shows vulnerable patients who present chronic anxiety or depressive symptoms and start to increase alcohol consumption in order to cope with negative emotions and stress (Alarm Mode hyperactivation). In this case, the Seek Mode is activated and leads to substance use in order to achieve balance. However, chronic stress and alcohol consumption predisposed the patients to develop addictive behaviors, which progressed to mental disorder as a result of emotional dysregulation and inhibitory control impairment.

Figure 2.

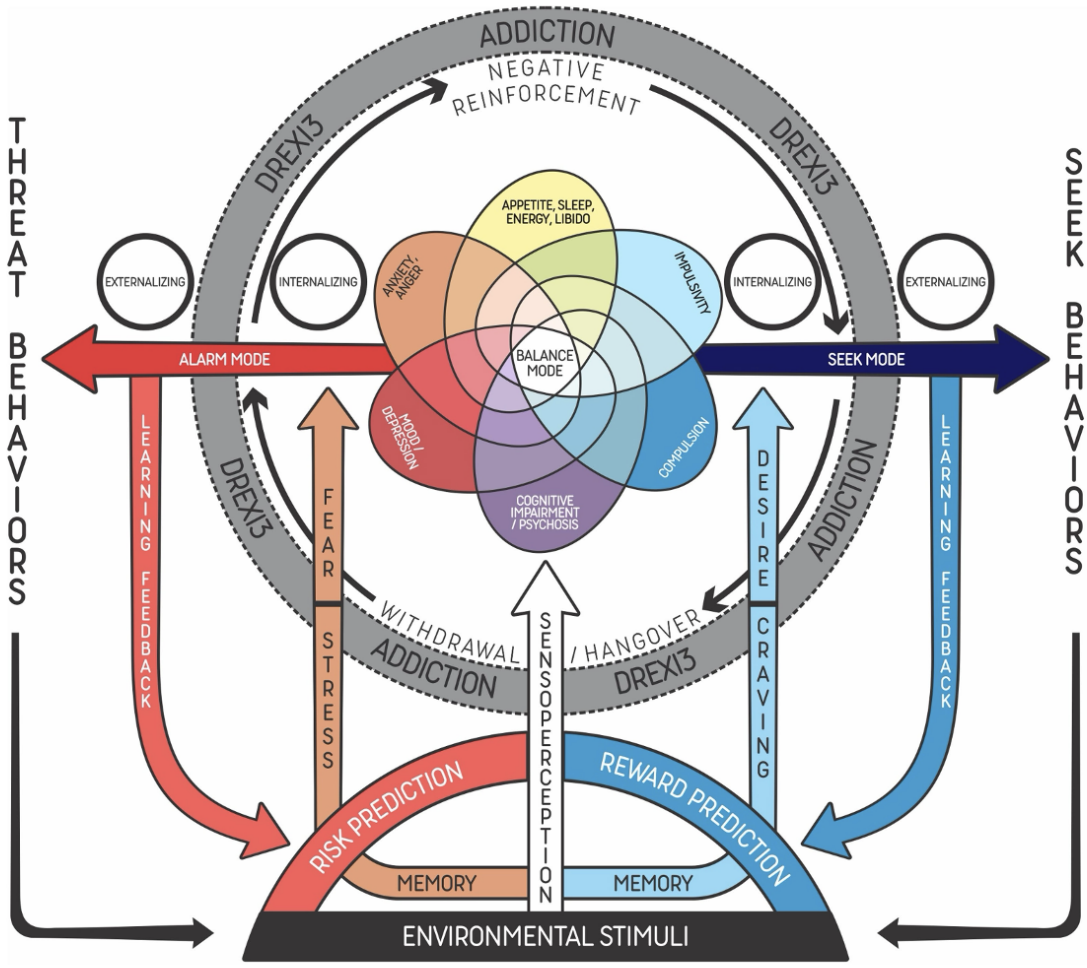


FIGURE 3

Addiction as dysregulation based on externalizing and internalizing phenomena of the three main modes of the predostatic mind (DREXI3). Representation of the functioning of individuals with an addictive disorder undergoing a severe situation, in which the mind tends to fluctuate between the Alarm Mode (in red) and the Seek Mode (in blue), struggling to keep balance. As the condition evolves, memories of risk associated with withdrawal symptoms are reinforced (negative feedback), and this prediction then triggers stress responses, leading to seeking behaviors that aim to achieve self-regulation. Due to strong memories of reward (learning feedback) related to the drug, the predictive mechanism activates substance craving as a means of reducing risks. This reinforces the emotional and behavioral cycle (in gray) associated with the increased activation of systems related to the Alarm and Seek Modes (allostasis) and decreased use of systems related to the typical animal Balance Mode (homeostasis). Fearful learning feedback is triggered in the Alarm Mode, leading to a prediction of risk and reactions of fight, fight, or freeze (stress). Conversely, rewarding learning feedback is increased every time regulation is easily achieved with strong stimuli (e.g., drug, video game, social media). During this process, there is an increase of psychopathological phenomena or symptoms in many domains of the transdiagnostic model, according to the type, frequency and severity of substance use.

Figure 3.

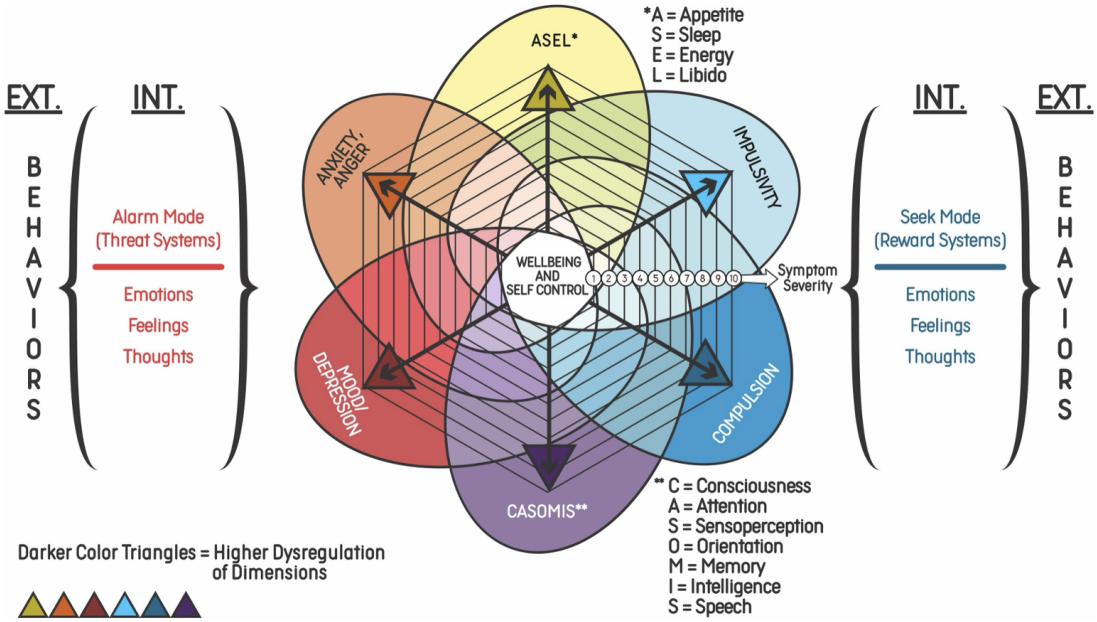


FIGURE 4
Six transdiagnostic dimensions of the DREXI3 model of dysregulation leading to externalizing and internalizing symptoms. Representation of the six dimensions of symptoms possibly observed in addiction: neurophysiological alterations, impulsivity; compulsion; cognitive impairment and psychosis; mood disorders/depression; and anxiety/anger. Each dimension is represented by a color and the severity of symptoms increases with the distance of a point from the center, which is a state of wellbeing and self-control. Activation of the Alarm and Seek Modes can cause both externalizing and internalizing symptoms, as represented by "EXT." and "INT." The severity of symptoms is related to the intensity of dysregulation. While emotions/feelings associated with the Alarm Mode are usually considered to be of negative valence and risk prediction, emotions/feelings in the Seek Mode are usually considered to be of positive valence and reward prediction.

Figure 4.

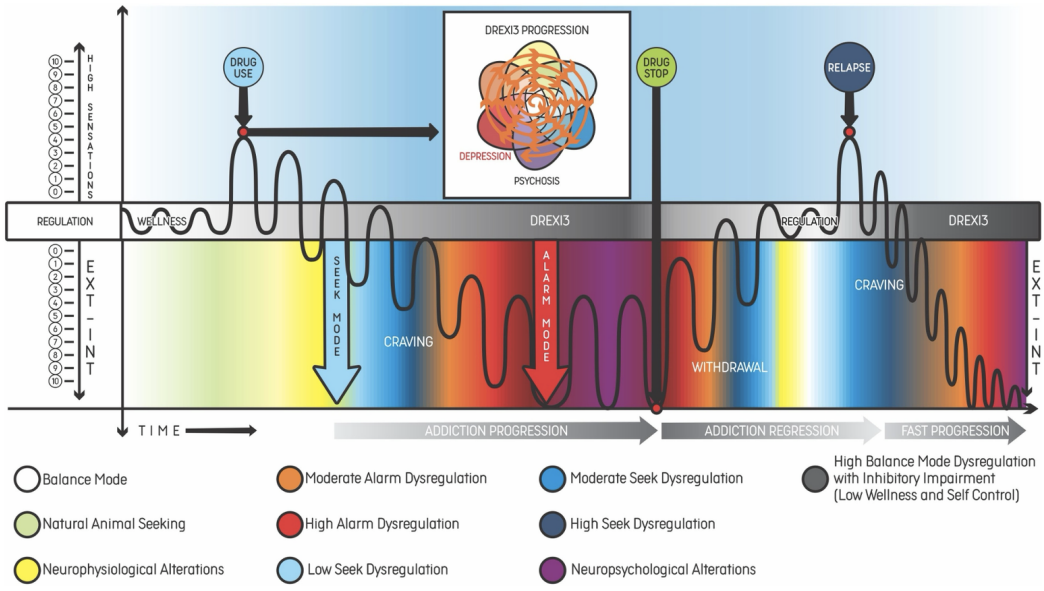


FIGURE 5
Example of addiction progression according to the DREXI3 model, beginning with drug experimentation in an individual with genetic predisposition. The progression of a healthy individual (patient 1 from Figure 2) after experimenting with cocaine and the relationship between disorder progression and the worsening of symptoms represented by the same colors of the DREXI3 model dimensions. The line represents adaptive (white/gray bar in the middle) and maladaptive responses (colored phenomena according to DREXI3). In the white box above the bar, centrifugal spiral arrows show the increase of psychiatric symptoms in all dimensions as the addiction disorder progresses, with decreased well-being and self-control until drug use stops. After the withdrawal phase, most of the psychiatric symptoms tend to improve towards regulation or homeostasis, provided no other relevant psychiatric comorbidities are present. Continuous drug use leads the patient to waves of an unstable regulation of the homeostasis, with emotional and behavioral dysregulation (suffering, inadequate and poor responses), which is also considered an allostatic state. Black "waves" in the figure represent drug consumption and its effects - such as internalizing (INT) and externalizing (EXT) phenomena. The variation of the waves represents the intensity of use - as well as its corresponding effects. The greater the dysregulation and the distance from the homeostatic state, the greater the allostatic load related to the disorder. For instance, in an individual diagnosed with alcohol use disorder, the mechanisms of addiction are installed, meaning that, after relapse, the process of dysregulation phenomena will occur more rapidly, as we can see in the final lines of the figure.

Figure 5.

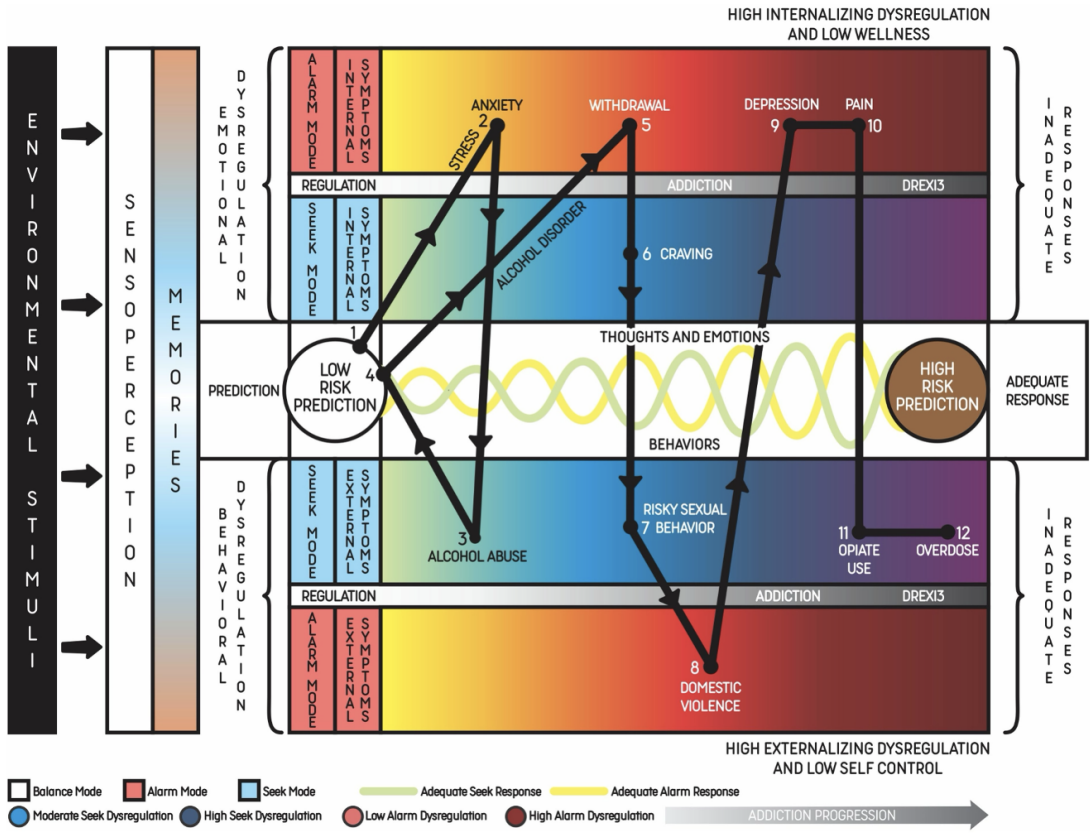


FIGURE 6

Example of alcohol use disorder progression over 10 years with increasing externalizing and internalizing phenomena until death by overdose. A 10-year natural progression of alcohol use disorder that evolved with internalized and externalized symptoms of the Alarm (red scale) and Seek (blue scale) Modes, beginning with comorbid anxiety disorder. This example represents young patients who are healthy (state of low-risk prediction) but start to face chronic stress due to financial problems, which activates the Alarm Mode and increases activation of the Seek Mode. Constant activation of the Alarm Mode leads to anxiety disorder. The patient keeps using alcohol to achieve the state of low-risk prediction, but his pattern of alcohol consumption increases, characterizing alcohol abuse. Excessive alcohol use indicates that the Seek Mode is more activated through a memory of reward related to relaxation and calmness. Although the individual may achieve the state of low-risk prediction for a period of time, alcohol withdrawal leads to the activation of the Alarm Mode again. During withdrawal, the patient develops craving, which can be considered an internalizing (thoughts and emotions) symptom of the increased Seek Mode activation. Each point of the graphic represents the main symptoms of the disorder along the evolution. This cycle leads to alcohol dependence, which is also associated with other externalizing symptoms such as aggressive behavior. In this phase, the patient may get involved in situations of violence and develop psychiatric comorbidities as a consequence of substance use. The association of other drug use disorders, like opiate use, may lead the patient to an overdose.

Figure 6.

7 CONSIDERAÇÕES FINAIS

Os transtornos aditivos permanecem entre os maiores desafios contemporâneos da Psiquiatria, não apenas por sua elevada prevalência e carga de doença, mas também pela dificuldade histórica de integrar, de forma operacional e clinicamente útil, os múltiplos mecanismos envolvidos em seu desenvolvimento e manutenção. Apesar dos avanços importantes nas neurociências, na psicofarmacologia e nas intervenções psicoterápicas, ainda existe uma distância considerável entre o conhecimento produzido em pesquisa básica e sua aplicação efetiva na prática clínica. Nesse cenário, esta tese buscou contribuir para a construção de um modelo mais dinâmico e transdiagnóstico para a compreensão e o tratamento das adições.

Ao longo deste trabalho, procurou-se desenvolver uma proposta teórica capaz de aproximar conceitos tradicionalmente estudados de forma fragmentada, como regulação emocional, neurobiologia do estresse, sistemas de recompensa, tomada de decisão, comportamento compulsivo, predição e homeostase. A partir do modelo da mente predostática e do conceito DREXI3, as adições passaram a ser compreendidas não apenas como um conjunto de sintomas categóricos ou como alterações isoladas do sistema de recompensa, mas como padrões crônicos de desregulação envolvendo diferentes modos de funcionamento mental relacionados busca, ameaça e equilíbrio.

Os modelos resultantes desta tese estão organizados em três artigos. O artigo "*Advanced Cognitive Emotional Regulation Therapy (ACERT) for Addiction Treatment*" representou uma tentativa inicial de organizar o tratamento das adições a partir de dimensões cognitivas e emocionais associadas à regulação do sofrimento psíquico. O segundo artigo, "*Proposing an integrative, dynamic and transdiagnostic model for addictions: dysregulation phenomena of the three main modes of the predostatic mind*", ampliou essa perspectiva ao propor uma compreensão mais abrangente e dinâmica das adições baseada na interação entre os três principais modos da mente predostática. O último artigo, "*BE-CERTIF(AI)D in Addiction Treatment: Personalized Regulation Therapy with Integrated Strategies using Artificial Intelligence*", incorporou elementos relacionados à personalização terapêutica, à psiquiatria de precisão e ao potencial uso de inteligência artificial na organização de intervenções mais individualizadas.

Mais do que propor uma nova nomenclatura, esta tese procurou desenvolver uma lógica organizacional capaz de facilitar a compreensão clínica de pacientes frequentemente marcados por elevada heterogeneidade sintomática, múltiplas comorbidades, sofrimento emocional persistente e baixa resposta aos tratamentos disponíveis. Nesse sentido, uma das

principais contribuições deste trabalho talvez tenha sido a tentativa de aproximar fenômenos biológicos, emocionais, cognitivos e comportamentais dentro de uma estrutura relativamente simples, inteligível e potencialmente aplicável na prática clínica.

Outro aspecto importante diz respeito à tentativa de compreender os comportamentos aditivos sob uma perspectiva menos fragmentada e menos centrada exclusivamente na substância utilizada. Ao considerar que emoções, pensamentos e comportamentos podem funcionar como respostas preditivas voltadas à busca de equilíbrio interno diante de sofrimento, ameaça ou privação, o modelo proposto amplia a possibilidade de compreender recaídas, compulsões e padrões disfuncionais de comportamento não apenas como “falhas de controle”, mas como processos complexos de adaptação mal sucedida. Essa perspectiva pode favorecer abordagens clínicas mais empáticas, menos estigmatizantes e potencialmente mais alinhadas às necessidades individuais dos pacientes.

Além disso, esta tese dialoga com movimentos contemporâneos da Psiquiatria que buscam superar limitações de modelos puramente categóricos. Embora sistemas diagnósticos tradicionais tenham desempenhado papel fundamental na padronização da prática clínica e da pesquisa, eles frequentemente apresentam dificuldades em captar a natureza dimensional, dinâmica e sobreposta dos transtornos mentais. A proposta apresentada ao longo deste trabalho não pretende substituir esses sistemas, mas contribuir para o desenvolvimento futuro de modelos complementares mais próximos da complexidade observada na prática clínica cotidiana.

Do ponto de vista translacional, esta tese também buscou refletir criticamente sobre um paradoxo frequente no campo das adições: apesar do grande volume de conhecimento neurobiológico produzido nas últimas décadas, os avanços terapêuticos permanecem relativamente modestos quando comparados a outras áreas da medicina. Nesse contexto, talvez seja necessário não apenas produzir mais dados, mas também desenvolver modelos teóricos capazes de organizar esses achados de forma clinicamente útil, favorecendo hipóteses mais integrativas e estratégias terapêuticas mais personalizadas.

Naturalmente, este trabalho apresenta limitações importantes. Grande parte das propostas desenvolvidas possui caráter teórico, narrativo e exploratório, exigindo futuras validações empíricas, refinamentos metodológicos e estudos longitudinais. Muitos dos conceitos apresentados ainda dependem de operacionalização mais objetiva e de instrumentos capazes de medir adequadamente os fenômenos descritos. Além disso, a complexidade dos transtornos mentais dificilmente pode ser plenamente explicada por um único modelo teórico. Assim, os modelos aqui propostos devem ser compreendidos como frameworks conceituais em

desenvolvimento, destinados principalmente à geração de hipóteses e à organização clínica de fenômenos complexos.

Entretanto, talvez uma das contribuições mais relevantes desta tese seja justamente a abertura de novas possibilidades de investigação. Futuras pesquisas poderão explorar validações clínicas e neurobiológicas dos modelos apresentados, desenvolvimento de instrumentos dimensionais, integração com biomarcadores, neuroimagem, modelos computacionais e inteligência artificial, além da construção de estratégias terapêuticas mais individualizadas baseadas em perfis de desregulação emocional, cognitiva e comportamental.

Também será fundamental investigar de que forma esses modelos podem contribuir para decisões terapêuticas mais precisas, melhor adesão ao tratamento, redução de recaídas e melhora funcional de pacientes com transtornos aditivos. Em um contexto no qual as adições tendem a se tornar progressivamente mais complexas e heterogêneas, abordagens integrativas e transdiagnósticas podem representar caminhos promissores para futuras transformações no campo.

Apesar das limitações descritas, os resultados desta tese trazem uma contribuição relevante e inovadora para a área das adições, partindo da compreensão de que pacientes com transtornos aditivos frequentemente vivem em intenso sofrimento, marcado por recaídas recorrentes, dificuldades emocionais, vulnerabilidades sociais e estigmatização persistente. Talvez compreender melhor os mecanismos pelos quais indivíduos tentam buscar equilíbrio diante desse sofrimento seja um passo importante para o desenvolvimento de modelos mais humanos, integrativos e personalizados em Psiquiatria. Mais do que encerrar respostas definitivas, este trabalho busca contribuir para a construção de novas perguntas, novos modelos e novas possibilidades de cuidado em saúde mental.

REFERÊNCIAS

1. Diagnostic and Statistical Manual of Mental Disorders : Fifth Edition Text Revision DSM-5-TR™. 1377.

2. Shaffer HJ, LaPlante DA, LaBrie RA, Kidman RC, Donato AN, Stanton MV. Toward a Syndrome Model of Addiction: Multiple Expressions, Common Etiology. Harv Rev Psychiatry. novembro de 2004;12(6):367–74. doi:10.1080/10673220490905705

3. Gabriels CM, Macharia M, Weich L. Psychiatric comorbidity among alcohol-dependent individuals seeking treatment at the Alcohol Rehabilitation Unit, Stikland Hospital. South Afr J Psychiatry. 16 de abril de 2019;25. doi:10.4102/sajpsychiatry.v25i0.1218

4. Grant BF, Saha TD, Ruan WJ, Goldstein RB, Chou SP, Jung J, et al. Epidemiology of *DSM-5* Drug Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions–III. JAMA Psychiatry. 1º de janeiro de 2016;73(1):39. doi:10.1001/jamapsychiatry.2015.2132

5. Iqbal MN, Levin CJ, Levin FR. Treatment for Substance Use Disorder With Co-Occurring Mental Illness. Focus. abril de 2019;17(2):88–97. doi:10.1176/appi.focus.20180042

6. Necho M, Belete A, Getachew Y. The prevalence and factors associated with alcohol use disorder among people living with HIV/AIDS in Africa: a systematic review and meta-analysis. Subst Abuse Treat Prev Policy. dezembro de 2020;15(1):63. doi:10.1186/s13011-020-00301-6

7. Necho M, Tsehay M, Seid M, Zenebe Y, Belete A, Gelaye H, et al. Prevalence and associated factors for alcohol use disorder among tuberculosis patients: a systematic review and meta-analysis study. Subst Abuse Treat Prev Policy. dezembro de 2021;16(1):2. doi:10.1186/s13011-020-00335-w

8. Lewer D, Freer J, King E, Larney S, Degenhardt L, Tweed EJ, et al. Frequency of health-care utilization by adults who use illicit drugs: a systematic review and meta-analysis. Addiction. junho de 2020;115(6):1011–23. doi:10.1111/add.14892

9. Šprah L, Dernovšek MZ, Wahlbeck K, Haaramo P. Psychiatric readmissions and their association with physical comorbidity: a systematic literature review. BMC Psychiatry. dezembro de 2017;17(1):2. doi:10.1186/s12888-016-1172-3

10. Constantinou N, Morgan CJA, Battistella S, O'Ryan D, Davis P, Curran HV. Attentional bias, inhibitory control and acute stress in current and former opiate addicts. Drug Alcohol Depend. 1º de junho de 2010;109(1–3):220–5. doi:10.1016/j.drugalcdep.2010.01.012

11. Ungless MA, Argilli E, Bonci A. Effects of stress and aversion on dopamine neurons: Implications for addiction. Neurosci Biobehav Rev. novembro de 2010;35(2):151–6. doi:10.1016/j.neubiorev.2010.04.006

12. Hossain M, Sultana A, Tasnim S, Fan Q, Ma P, McKyer ELJ, et al. Prevalence of mental disorders among people who are homeless: An umbrella review. Int J Soc Psychiatry.

13. Van Draanen J, Tsang C, Mitra S, Karamouzian M, Richardson L. Socioeconomic marginalization and opioid-related overdose: A systematic review. Drug Alcohol Depend. setembro de 2020;214:108127. doi:10.1016/j.drugalcdep.2020.108127

14. Sinha R. Chronic Stress, Drug Use, and Vulnerability to Addiction. Ann N Y Acad Sci. outubro de 2008;1141(1):105–30. doi:10.1196/annals.1441.030

15. Anderson AC, Youssef GJ, Robinson AH, Lubman DI, Verdejo-Garcia A. Cognitive boosting interventions for impulsivity in addiction: a systematic review and meta-analysis of cognitive training, remediation and pharmacological enhancement. Addiction. dezembro de 2021;116(12):3304–19. doi:10.1111/add.15469

16. Mohammadpoorasl A, Nedjat S, Fakhari A, Yazdani K, Foroushani AR, Fotouhi A. Substance Abuse in High School Students in Association with Socio-Demographic Variables in Northwest of Iran. V. 41. 2012;41.

17. Sliedrecht W, De Waart R, Witkiewitz K, Roozen HG. Alcohol use disorder relapse factors: A systematic review. Psychiatry Res. agosto de 2019;278:97–115. doi:10.1016/j.psychres.2019.05.038

18. A T McLellan, L Luborsky, G E Woody, C P O'Brien. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. J Nerv Ment Dis. 1980;168.

19. Kessler F, Cacciola J, Alterman A, Faller S, Souza-Formigoni ML, Cruz MS, et al. Psychometric properties of the sixth version of the Addiction Severity Index (ASI-6) in Brazil. 10.

20. LABOR UNOODA. WORLD DRUG REPORT 2021 (SET OF 5 BOOKLETS). S.l.: UNITED NATIONS; 2022.

21. UNIVERSIDADE FEDERAL DE SÃO PAULO (UNIFESP). Terceiro Levantamento Nacional de Álcool e Drogas (LENAD III): Caderno Temático – Resultados Consumo de Álcool na População Brasileira. São Paulo: UNIFESP; 2025.

22. Rehm J, Shield KD. Global Burden of Disease and the Impact of Mental and Addictive Disorders. Curr Psychiatry Rep. fevereiro de 2019;21(2):10. doi:10.1007/s11920-019-0997-0

23. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. outubro de 2020;396(10258):1204–22. doi:10.1016/S0140-6736(20)30925-9

24. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. novembro de 2018;392(10159):1736–88. doi:10.1016/S0140-6736(18)32203-7

25. Volkow ND. Addiction, a Disease of Compulsion and Drive: Involvement of the Orbitofrontal Cortex. Cereb Cortex. 1º de março de 2000;10(3):318–25. doi:10.1093/cercor/10.3.318

26. Volkow ND, Fowler JS, Wang GJ. Role of dopamine in drug reinforcement and addiction in humans: results from imaging studies: Behav Pharmacol. setembro de 2002;13(5):355–66. doi:10.1097/00008877-200209000-00008

27. Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. J Clin Invest. 15 de maio de 2003;111(10):1444–51. doi:10.1172/JCI18533

28. Volkow ND, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. Longo DL, organizador. N Engl J Med. 28 de janeiro de 2016;374(4):363–71. doi:10.1056/NEJMra1511480

29. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. agosto de 2016;3(8):760–73. doi:10.1016/S2215-0366(16)00104-8

30. Hall W, Carter A, Forlini C. The brain disease model of addiction: is it supported by the evidence and has it delivered on its promises? Lancet Psychiatry. janeiro de 2015;2(1):105–10. doi:10.1016/S2215-0366(14)00126-6

31. Volkow ND, Koob G. Brain disease model of addiction: why is it so controversial? Lancet Psychiatry. agosto de 2015;2(8):677–9. doi:10.1016/S2215-0366(15)00236-9

32. Khantzian J. Focus on Heroin and Cocaine Dependence. Am J Psychiatry. 1985;6.

33. Khantzian EJ. The Self-Medication Hypothesis of Substance Use Disorders: A Reconsideration and Recent Applications. Harv Rev Psychiatry. janeiro de 1997;4(5):231–44. doi:10.3109/10673229709030550

34. Khantzian EJ. Commentary: It Is Not About Supply, It Is About Demand: Why the Self-Medication Hypotheses Is Still So Important. Am J Addict. julho de 2021;30(4):301–4. doi:10.1111/ajad.13111

35. Loreto BBL, Sordi AO, Ruwel AG, Falleiro CF, De Souza CS, Daitschman D, et al. Teorias homeostáticas das adições: uma revisão narrativa. Rev Bras Psicoter. 2024;26(1):91–104. doi:10.5935/2318-0404.20240008

36. Billman GE. Homeostasis: The Underappreciated and Far Too Often Ignored Central Organizing Principle of Physiology. Front Physiol. 10 de março de 2020;11:200. doi:10.3389/fphys.2020.00200

37. Koob G. Drug Addiction, Dysregulation of Reward, and Allostasis. Neuropsychopharmacology. fevereiro de 2001;24(2):97–129. doi:10.1016/S0893-133X(00)00195-0

38. World Health Organization. International Classification of Diseases 11th Revision [Internet]. [citado 27 de maio de 2026]. Disponível em: https://icd.who.int/browse/2026-01/mms/en

39. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. J Abnorm Psychol. maio de 2017;126(4):454–77. doi:10.1037/abn0000258

40. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. Am J Psychiatry. julho de 2010;167(7):748–51. doi:10.1176/appi.ajp.2010.09091379

41. McLellan T, Luborsky L, Woody GE, O'Brien CP. An Improved Diagnostic Evaluation Instrument for Substance Abuse Patients The Addiction Seveity Index. J Nerv Ment Dis. 1980;168(1).

42. Robison AJ, Nestler EJ. Transcriptional and epigenetic mechanisms of addiction. Nat Rev Neurosci. novembro de 2011;12(11):623–37. doi:10.1038/nrn3111

43. Piazza PV, Deroche-Gamonet V. A multistep general theory of transition to addiction. Psychopharmacology (Berl). outubro de 2013;229(3):387–413. doi:10.1007/s00213-013-3224-4

44. McPheeters, M., O'Connor, E.A., Riley, S., Kennedy, S.M., Voisin, C., Kuznacic, K., et al. Pharmacotherapy for Alcohol Use Disorder - PMC. Pharmacother Alcohol Use Disord. 7 de novembro de 2023. doi:10.1001/jama.2023.19761 PubMed PMID: 37934220; PubMed Central PMCID: PMC10630900.

45. Skinner MD, Lahmek P, Pham H, Aubin HJ. Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis. Laks J, organizador. PLoS ONE. 10 de fevereiro de 2014;9(2):e87366. doi:10.1371/journal.pone.0087366

46. Patel AR, Panchal JR, Desai CK. Efficacy of varenicline versus bupropion for smoking cessation: A systematic review and meta-analysis of randomized controlled trials. Indian J Psychiatry. maio de 2023;65(5):526–33. doi:10.4103/indianjpsychiatry.indianjpsychiatry_218_22

47. Rábade-Castedo C, De Granda-Orive JI, Riesco-Miranda JA, De Higes-Martínez E, Ramos-Pinedo Á, Cabrera-César E, et al. Clinical Practice Guideline of Spanish Society of Pneumology and Thoracic Surgery (SEPAR) on Pharmacological Treatment of Tobacco Dependence 2023. Arch Bronconeumol. outubro de 2023;59(10):651–61. doi:10.1016/j.arbres.2023.07.024

48. James DL, Jowza M. Treating Opioid Dependence: Pain Medicine Physiology of Tolerance and Addiction. Clin Obstet Gynecol. março de 2019;62(1):87–97. doi:10.1097/GRF.0000000000000422

49. Helm Ii S. Opioid Antagonists, Partial Agonists, andAgonists/Antagonists: The Role of OfficeBased Detoxification. Pain Physician. 14 de março de 2008;2;11(3;2):225–35. doi:10.36076/ppj.2008/11/225

50. Spirito A, Monti PM, Barnett NP, Colby SM, Sindelar H, Rohsenow DJ, et al. A randomized clinical trial of a brief motivational intervention for alcohol-positive adolescents treated in an emergency department. J Pediatr. setembro de 2004;145(3):396–402. doi:10.1016/j.jpeds.2004.04.057

51. McRae AL, Budney AJ, Brady KT. Treatment of marijuana dependence: a review of the literature. J Subst Abuse Treat. junho de 2003;24(4):369–76. doi:10.1016/S0740-5472(03)00041-2

52. Jhanjee S. Evidence Based Psychosocial Interventions in Substance Use. Indian J Psychol Med. abril de 2014;36(2):112–8. doi:10.4103/0253-7176.130960

53. Boness CL, Votaw V, Schwebel FJ, Moniz-Lewis DIK, McHugh RK, Witkiewitz K. An Evaluation of Cognitive Behavioral Therapy for Substance Use Disorder: A Systematic Review and Application of the Society of Clinical Psychology Criteria for Empirically Supported Treatments [Internet]. 2022 [citado 28 de julho de 2024]. Disponível em: https://osf.io/rpwh9 doi:10.31234/osf.io/rpwh9

54. Marlatt GA, Donovan DM, organizadores. Relapse prevention: maintenance strategies in the treatment of addictive behaviors. 2nd ed. New York: Guilford Press; 2005. 416 p.

55. Ainscough TS, McNeill A, Strang J, Calder R, Brose LS. Contingency Management interventions for non-prescribed drug use during treatment for opiate addiction: A systematic review and meta-analysis. Drug Alcohol Depend. setembro de 2017;178:318–39. doi:10.1016/j.drugalcdep.2017.05.028

56. Rodas JD, Sorkhou M, George TP. Contingency Management for Treatment of Cannabis Use Disorder in Co-Occurring Mental Health Disorders: A Systematic Review. Brain Sci. 23 de dezembro de 2022;13(1):36. doi:10.3390/brainsci13010036

57. Lo Coco G, Melchiori F, Oieni V, Infurna MR, Strauss B, Schwartze D, et al. Group treatment for substance use disorder in adults: A systematic review and meta-analysis of randomized-controlled trials. J Subst Abuse Treat. abril de 2019;99:104–16. doi:10.1016/j.jsat.2019.01.016

58. Kelly JF, Humphreys K, Ferri M. Alcoholics Anonymous and other 12-step programs for alcohol use disorder. Cochrane Drugs and Alcohol Group, organizador. Cochrane Database Syst Rev. 11 de março de 2020. doi:10.1002/14651858.CD012880.pub2

59. Khantzian EJ. The Self-Medication Hypothesis of Substance Use Disorders: A Reconsideration and Recent Applications. Harv Rev Psychiatry. janeiro de 1997;4(5):231–44. doi:10.3109/10673229709030550

60. Aldao A, Nolen-Hoeksema S, Schweizer S. Emotion-regulation strategies across psychopathology: A meta-analytic review. Clin Psychol Rev. março de 2010;30(2):217–37. doi:10.1016/j.cpr.2009.11.004

61. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci. novembro de 2011;12(11):652–69. doi:10.1038/nrn3119

62. Everitt BJ, Robbins TW. Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On. Annu Rev Psychol. 4 de janeiro de 2016;67(1):23–50. doi:10.1146/annurev-psych-122414-033457

63. Koob GF, Le Moal M. Addiction and the Brain Antireward System. Annu Rev Psychol. 1º de janeiro de 2008;59(1):29–53. doi:10.1146/annurev.psych.59.103006.093548

64. Unidade de Pesquisa em Álcool e Drogas (UNIAD). Caderno Temático LENAD III: Consumo de Cocaína e Crack. São Paulo: UNIFESP; 2025.

65. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: Precision Medicine for Psychiatry. Am J Psychiatry. abril de 2014;171(4):395–7. doi:10.1176/appi.ajp.2014.14020138

66. Fried EI. Studying Mental Health Problems as Systems, Not Syndromes.

67. Borsboom D, Van Der Maas HLJ, Dalege J, Kievit RA, Haig BD. Theory Construction Methodology: A Practical Framework for Building Theories in Psychology. Perspect Psychol Sci. julho de 2021;16(4):756–66. doi:10.1177/1745691620969647

68. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 30 de setembro de 2021;n2061. doi:10.1136/bmj.n2061

69. Cannon WB. The Wisdom of the Body. New York: Norton & Company; 1932.

70. Cooper SJ. From Claude Bernard to Walter Cannon. Emergence of the concept of homeostasis. Appetite. novembro de 2008;51(3):419–27. doi:10.1016/j.appet.2008.06.005

71. Rosenblueth A, Wiener N, Bigelow J. Behavior, Purpose and Teleology. Philos Sci. 1943;10(1):18–24.

72. Yon D, Heyes C, Press C. Beliefs and desires in the predictive brain. Nat Commun. dezembro de 2020;11(1):4404. doi:10.1038/s41467-020-18332-9

73. Noble D. Evolution viewed from physics, physiology and medicine. Interface Focus. 6 de outubro de 2017;7(5):20160159. doi:10.1098/rsfs.2016.0159

74. Brüne M, Belsky J, Fabrega H, Feierman HR, Gilbert P, Glantz K, et al. The crisis of psychiatry — insights and prospects from evolutionary theory. World Psychiatry. fevereiro de 2012;11(1):55–7. doi:10.1016/j.wpsyc.2012.01.009