UNIVERSIDADE D
COIMBRA

Mariana da Costa Soares

Relatório de Estágio sob a orientação do Dr. Hélvio Bastos e Monografia intitulada "Therapeutic management of alcohol addiction and underlying physiopharmacological mechanisms" sob orientação da Professora Doutora Sónia Silva, referentes à Unidade Curricular "Estágio", apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

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Coimbra, 11 de julho de 2023.

Mariana da Costa Soares

(Mariana da Costa Soares)

Agradecimentos

A vocês, mãe e pai, que sempre fizeram tudo por mim, para que eu pudesse seguir os meus sonhos, sem que nunca me faltasse amor, apoio e carinho. Obrigada por serem o melhor exemplo que podia ter, o amor por vocês não tem medida.

A ti mana, que apesar de todos os contratempos da vida, nunca me deixaste de apoiar e sentes todas as minhas conquistas e felicidades como se fossem tuas. Um dia vou ser como tu, prometo.

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Esta monografia é dedicada a vocês.

Um gigante obrigada!

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PARTE I

Relatório de Estágio em Farmácia Comunitária

Farmácia Gomes da Costa

Oliveira de Azeméis

Sob orientação do Dr. Hélvio Bastos

ABREVIATURAS

DCI: Denominação Comum Internacional

FGC: Farmácia Gomes da Costa

MICF: Mestrado Integrado em Ciências Farmacêuticas

MSRM: Medicamentos Sujeitos a Receita Médica

SWOT: *Strengths, Weaknesses, Opportunities, Threats*

1. INTRODUÇÃO

Nas últimas duas décadas, o papel do farmacêutico tem sido crucial para a sociedade, desempenhando um amplo e fundamental espetro de atividades para a Saúde Pública. O farmacêutico desempenha um papel vital na segurança e efetividade das terapêuticas dos utentes, permitindo que estes se sintam acompanhados e bem orientados quanto ao uso adequado dos medicamentos.

Ao longo de 5 anos no Mestrado Integrado em Ciências Farmacêuticas (MICF), adquirimos conhecimento em diversas áreas, tanto a nível teórico como prático, e tivemos contacto com diferentes campos da ciência e saúde, que nos permitiram obter uma base de conhecimento e desenvolver o nosso espírito crítico. O estágio curricular, como última etapa do Mestrado, proporciona uma experiência prática num ambiente farmacêutico do "mundo real", permitindo aplicar os conhecimentos e competências adquiridas nas unidades curriculares em situações reais. Além disso, contactamos com procedimentos que não são tipicamente desenvolvidos num ambiente académico tradicional.

No presente relatório, referente ao estágio realizado na Farmácia Gomes da Costa (FGC) em Oliveira de Azeméis, é apresentada uma análise SWOT (*Strengths*, Weaknesses, *Opportunities*, *Threats*), com o intuito de identificar e analisar os pontos fortes, pontos fracos, oportunidades e ameaças deste. Também são relatados casos práticos vivenciados durante o período de estágio, que contribuíram para uma melhor consolidação e desenvolvimento dos conhecimentos adquiridos ao longo do percurso académico. O estágio, sob a orientação do Doutor Hélvio Bastos, teve início dia 9 de janeiro de 2023 e término dia 31 de maio de 2023, perfazendo um total de 810 horas.

2. FARMÁCIA GOMES DA COSTA

A Farmácia Gomes da Costa, localizada na Rua António Alegria , é uma das farmácias principais em Oliveira de Azeméis. Está situada numa rua pedonal, o que lhe confere uma elevada visibilidade, e atende um grupo de utentes bastante heterogéneo. Essa diversidade proporcionou-me a oportunidade de interagir com diferentes pessoas, personalidades, patologias e tratamentos, permitindo-me adquirir experiência na adaptação do atendimento a cada indivíduo que contactasse.

A FGC possui 5 balcões de atendimento individualizados, sendo um deles localizado próximo à área de puericultura e outro junto aos suplementos alimentares. A equipa é composta por 7 profissionais, incluindo o Diretor Técnico. O seu horário de funcionamento é das 9h às 19h30 de segunda a sexta e das 9h às 13h aos sábados, com exceção dos dias de serviço, que alternava com as outras 3 farmácias de Oliveira de Azeméis. Na Análise SWOT são apresentadas as diferentes funções desempenhadas e o sistema informático utilizado, o Sifarma® (antigo e novo módulo).

3. ANÁLISE SWOT

Figura 1. *Análise SWOT do estágio realizado na FGC.*

3.1 PONTOS FORTES (*STRENGTHS*)

3.1.1 Boa Integridade na Equipa

No decorrer do meu estágio, tive a oportunidade de integrar uma equipa comunicativa e eficiente, cujo objetivo coletivo era a qualidade e excelência do seu trabalho, bem como o bem-estar e satisfação do utente. Sendo a única estagiária na farmácia, pude experenciar de forma privilegiada os diferentes serviços disponibilizados, sempre beneficiando de um excelente acompanhamento e apoio nas tarefas que desempenhei. Entre os membros da equipa, existia uma boa relação de entreajuda, com uma comunicação clara e respeito mútuo, o que proporcionava um ambiente propício para colocar questões, esclarecer dúvidas e obter auxílio em determinadas situações. Além disto, este ambiente de união na equipa contribuía para a boa qualidade do atendimento e demais funções, permitindo que todos os colaboradores, incluindo eu, apesar de ser estagiária, estivessem melhor informados e atualizados, transmitindo esse conhecimento aos utentes.

Sinto que esta boa integridade na equipa, juntamento com a experiência de cada colaborador, tanto dos farmacêuticos como dos técnicos de farmácia, trouxe vantagens significativas para a minha aprendizagem e desenvolvimento, tanto a nível profissional como pessoal. Esta vivência permitiu-me adquirir valores de cooperação, transparência e responsabilidade, fundamentais para uma prática farmacêutica exemplar.

3.1.2 Facilidade de utilização do Sifarma 2000®

O Sifarma 2000® é um sistema informático de gestão de farmácias que oferece uma ampla gama de recursos e funcionalidades, proporcionando maior segurança e eficiência nas atividades realizades pelas farmácias.

Na FGC, utiliza-se o Sifarma 2000® como software principal para executar diversas tarefas, como gestão de stocks, receção e gestão de encomendas, faturação, atendimento e dispensa de medicamentos, entre outras. A facilidade de uso desse sistema operacional beneficiou a minha aprendizagem, e as características do programa contribuiram para aprimorar a segurança e a qualidade no momento do atendimento. Através do Sifarma 2000®, antes do término do atendimento, existe um passo de verificação dos medicamentos e é possível verificar a autenticidade dos mesmos (através de um sistema de rastreio) e ter acesso a informações relevantes sobre eles. Isso proporciona maior confiança tanto para os profissionais da farmácia quanto para os utentes, garantindo um serviço de qualidade e segurança no fornecimento dos medicamentos.

3.1.3 Funções diversificadas e variados serviços disponibilizados pela farmácia

A FGC disponibiliza diversos serviços orientados para os seus utentes, com o foco em garantir a sua satisfação e saúde. Sendo a única estagiária, tive a oportunidade de vivenciar cada um desses serviços e repeti-los várias vezes, o que me permitiu corrigir os meus erros e melhorar o meu desempenho e prática. Ao contrário do pensamento generalizado de que a farmácia comunitária se resume a uma simples venda de medicamentos, nos "bastidores" existem várias tarefas de backoffice que são indispensáveis ao seu funcionamento.

Inicialmente, o estágio centrou-se na compreensão e aprendizagem do módulo de gestão e receção de encomendas, das margens de venda ao público nos medicamentos de venda livre e da gestão de *stocks*. Pude adquirir competências e conhecimentos que serão uma mais-valia para a área de gestão no futuro.

Posteriormente, comecei por assistir a atendimentos e aconselhamentos, com o objetivo de adquirir mais experiência e confiança e de contactar com diferentes casos práticos. No final do período do estágio, tive a oportunidade de fazer os atendimentos e aconselhamentos por conta própria, de acordo com os meus conhecimentos e espírito crítico, acompanhada pelo farmacêutico responsável. Nesta fase, ganhei mais confiança e pude demonstrar os conhecimentos adquiridos tanto na faculdade como durante os meses de estágio. Também aprendi a fazer a verificação/controlo dos prazos de validade, realizar devoluções e as respetivas regularizações.

A FGC oferece também outros serviços complementares, como a medição da pressão arterial, glicémia, colesterol total e triglicerídeos. Além disso, durante o período do estágio, participei ativamente na realização de vários rastreios de controlo desses parâmetros e do risco cardiovascular.

3.1.4 Vasto aconselhamento dermocosmético e de suplementação

Ao longo do meu estágio, contactei com diferentes marcas de dermocosméticos e adquiri confiança no aconselhamento desses produtos. Existiam vários expositores direcionados para essa temática, a qual despertava muito interesse por parte dos utentes da farmácia. A equipa estava bem treinada para aconselhar esse tipo de produtos, graças a formações externas e às formações ministradas pelos delegados durante as suas visitas à farmácia. O material facultado pelas próprias marcas, como folhetos ou cartazes, permitia verificar e confirmar rapidamente os aspetos relevantes de cada produto e as suas principais

indicações. Assim, adquiri conhecimentos nesssa área ao longo destes meses, o que me permitiu ganhar autonomia no aconselhamento deste segmento.

A FGC também dispõe de uma ampla gama de suplementos alimentares, com diferentes formas farmacêuticas, de modo a satisfazer as diversas necessidades dos seus utentes. Estes suplementos têm como objetivo complementar o regime alimentar normal, sendo fontes concentradas de nutrientes ou outras substâncias (*Decreto-Lei n.º 118/2015, de 23 de junho | DR*, [s.d.]). Eram muito requisitados pelos utentes, especialmente quando estes se sentiam cansados fisicamente e mentalmente. Além disso, havia outras razões para a sua elevada procura, como distúrbios do sono, complementação nutricional para crianças ou situações relacionadas com a menopausa, entre outras.

3.2 PONTOS FRACOS (*WEAKNESSES*)

3.2.1 Aconselhamento de medicamentos de uso veterinário

Apesar de a FGC possuir uma ampla variedade de produtos veterinários e de a unidade curricular "Preparações de Uso Veterinário" nos fornecer conhecimentos sobre esse tema, durante o estágio, não me senti devidamente preparada para aconselhar e esclarecer possíveis dúvidas dos utentes em relação a esse tipo de produtos.

No entanto, a apresentação de receitas veterinárias era frequente, o que me permitiu conhecer e entrar em contacto com produtos que desconhecia, ganhando assim experiência e conhecimento nessa área.

3.2.2 Preparação de medicamentos manipulados

Os medicamentos manipulados podem ser definidos como Fórmulas Magistrais (preparados de acordo com uma receita médica) ou Preparados Oficinais (preparados de acordo com a Farmacopeia ou Formulário), sendo preparados e dispensados sob a responsabilidade de um farmacêutico, seguindo as "Boas práticas a observar na preparação de medicamentos manipulados" (*Medicamentos manipulados*, [s.d.]). Estes medicamentos desempenham um papel importante ao preencher possíveis lacunas terapêuticas que exigem uma adaptação personalizada para cada utente.

Na FGC, este serviço não era realizado internamente. Sempre que surgia uma prescrição ou um pedido de um medicamento manipulado, a farmácia entrava em contacto com a Farmácia Barreiros, localizada no Porto, que procedia à satisfação do pedido.

Infelizmente, isso limitou a minha experiência e envolvimento direto com esta vertente farmacêutica, que é a preparação de medicamentos manipulados.

3.2.3 Dificuldade na associação de princípios ativos e marcas

Durante o meu percurso académico, nas várias cadeiras, abordávamos os diferentes medicamentos com base na sua Denominação Comum Internacional (DCI), ou seja, o nome do princípio ativo. Logo no início do estágio na FGC, apercebi-me de que os utentes se referiam aos seus medicamentos pelo nome da marca e não pelo DCI, devido à facilidade que tinham em memorizar a embalagem e o que lá estava escrito.

Na faculdade, estamos habituados a utilizar apenas o nome do princípio ativo, e no estágio não tinha uma noção completo e um grande conhecimento das diversas marcas disponíveis no mercado farmacêutico. Assim, com exceção das situações de prescrições eletrónicas em que o sistema indica as marcas correspondentes, inicialmente associar os princípios ativos às marcas representou um desafio. Com o tempo, tornou-se uma tarefa muito mais fácil e mais intuitiva, mas sinto que foi uma das partes do estágio em que encontrei mais dificuldades.

3.3 OPORTUNIDADES (*OPPORTUNITIES*)

3.3.1 Dispensa de medicamentos hospitalares

Durante o estágio, tive a oportunidade de efetuar a dispensa de medicamentos hospitalares, embora esta fosse direcionada apenas a um utente da farmácia. Com a aprovação da proposta que permite a dispensa de medicação hospitalar em Unidades de Saúde de Proximidade, quer sejam Unidades de Cuidados de Saúde Primários ou Farmácias Comunitárias (Seara.com, [s.d.]), vários utentes beneficiaram do acesso facilitado à terapêutica, melhorando, assim, a adesão à mesma. Sempre sob a supervisão de um farmacêutico, entrei em contacto com fármacos com os quais tradicionalmente não teria contacto, adquirindo assim novos conhecimentos acerca de terapêuticas e patologias menos frequentes.

3.3.2 Formações com marcas e contacto com os respetivos delegados

O mundo da ciência e da saúde está em constante evolução, sendo um dos deveres do farmacêutico estar informado acerca dos novos princípios ativos e formulações que continuam a surgir no mercado farmacêutico.

As diversas marcas e laboratórios facilitam o primeiro contacto com os novos produtos, através das suas apresentações e formações destinadas aos colaboradores da farmácia. Durante o estágio, tive a oportunidade de participar em várias formações, recordar conceitos esquecidos e relacioná-los com os diferentes produtos/marcas disponíveis. Com as visitas dos delegados de informação médica, pude conhecer os novos produtos do mercado de diferentes marcas, as respetivas posologias e quando os recomendar/ aconselhar. Também assisti a reuniões com delegados de laboratórios de genéricos, onde tive uma visão mais aprofundada sobre a gestão de uma farmácia e os conceitos envolvidos. Estes tópicos são pouco abordadas no Mestrado Integrado, por isso considerei esta experiência enriquecedora, uma vez que adquiri mais conhecimentos sobre como avaliar as diferentes promoções e bonificações, e determinar o que seria mais vantajoso para a farmácia.

Além disso, tive a oportunidade de assistir a uma formação da marca D'Aveia, realizada no Axis Porto Hotel, onde adquiri bastante conhecimento sobre os seus produtos, suas principais características e os momentos mais adequados para o seu aconselhamento e utilização.

3.3.3 Aprendizagem obtida com prescrições médicas e respetivos diagnósticos

Os conhecimentos adquiridos ao longo dos 5 anos de Mestrado são essenciais para o nosso futuro como farmacêuticos, permitindo-nos tornar mais sábios e aplicar essas informações em casos práticos do mundo real. No que diz respeito aos medicamentos sujeitos a receita médica (MSRM), a prescrição médica desempenha um papel crucial, proporcionando-nos a oportunidade de lidar com diferentes tratamentos e posologias, conhecer ou recordar doenças menos comuns e os respetivos tratamentos atuais. É importante mencionar que o campo da ciência e saúde está em constante atualização. Como profissionais de saúde experientes (experiência adquirida ao longo dos anos de prática), é nossa responsabilidade detetar possíveis erros na prescrição e confirmá-los juntos do médico responsável, de uma forma adequada e respeitosa, sem ultrapassar a autoridade médica.

Assim, pude pessoalmente compreender o papel do farmacêutico na segurança dos tratamentos, ampliar e relembrar conceitos discutidos e aplicá-los no mundo real.

3.4 AMEAÇAS (*THREATS*)

3.4.1 Aumento dos preços

No início de 2023, o Ministério da Saúde anunciou certas medidas, incluindo um aumento ligeiro nos preços (Seara.com, [s.d.]), com o intuito de combater a rutura de stocks sentida nas farmácias. Além disso, os custos relacionados com a disponibilidade de matérias-primas, o seu transporte, aquisição e custos energéticos contribuíram para esse aumento. Embora justificado e com um aumento pequeno, os utentes sentiram impacto no seu dia-a-dia, uma vez que, adjacente a este, ocorreram aumentos noutros campos, como alimentação e transportes. Além disso, os medicamentos de venda livre sofreram aumento nos custos de compra, o que levou a um aumento simultâneo nos seus preços de venda ao público. Estas alterações fazem com que os utentes tenham um poder de compra inferior ao que tinham anteriormente, impossibilitando, por vezes, que usufruam plenamente do aconselhamento prestado, devido à impossibilidade de adquirir os produtos.

3.4.2 Medicamentos esgotados

Ao longo do estágio, deparei-me com uma questão de extrema preocupação: a falta de determinados medicamentos e a ausência de previsão para o seu restabelecimento. A situação agravava-se à medida que os *stocks* de certos fármacos se esgotavam, levando à interrupção do tratamento de alguns utentes e acarretando consequências negativas para a sua saúde. Ao efetuar encomendas, deparavámo-nos com a mensagem de "indisponibilidade", o que gerava frustação e preocupação do utente. A falta de resposta por parte da farmácia criava desconfiança no utente, afetando assim a relação utente-farmácia existente, mesmo com as explicações fornecidas. Esta problemática gerava um sentimento de impotência nos farmacêuticos, que não conseguiam garantir as solicitações dos utentes. Além disso, resultava em dificuldades na adesão às diferentes terapêuticas afetadas e numa consequente diminuição das vendas da farmácia.

3.4.3 Receitas manuais

Atualmente, devido a certas situações como falhas no sistema informático ou, mais recentemente, a falta de disponibiblidade de certos medicamentos que não permite a prescrição eletrónica dos mesmos, os médicos recorrem a receitas manuais. Embora essas situações ocorram com menos frequência, é crucial saber verificar as características que tornam essas receitas válidas - validade de 30 dias a partir da data da prescrição, limite máximo

de 4 unidades (mesmo que sejam de medicamentos diferentes), presença obrigatória da vinheta do médico, entre outras. Tudo isso, juntamente com a ilegibilidade que certas receitas possuem, dificulta o processo de atendimento e pode levar a possíveis erros na dispensa da medicação, como trocas na dosagem ou na forma farmacêutica. Durante o estágio, tive a oportunidade de colocar em prática a verificação correta do receituário, a fim de evitar erros no futuro.

4. CASOS CLÍNICOS

Caso Clínico 1

Uma utente, do sexo feminino, com cerca de 30 anos, dirigiu-se à farmácia, queixando-se de infeções urinárias recorrentes. Recentemente, tomou um antibiótico para tratar uma infeção e procurava algo que prevenisse futuras infeções, uma vez que são situações extremamente desagradáveis e desconfortáveis.

Uma infeção urinária corresponde a uma infeção no trato urinário, ou seja, quando há presença de bactérias que, dependendo da sua localização, causam sintomas como urgência miccional, dor ou ardor a urinar, dificuldade em urinar e em pequenas quantidades, urina turva e com cheiro fétido. Pode-se tratar de uma pielonefrite, cistite ou uretrite, se a sua localização for o rim, a bexiga ou a uretra, respetivamente. Normalmente, no caso de uma infeção simples, o tratamento baseia-se no uso de antibióticos, anti-inflamatórios e hidratação. O uso de antibióticos pode levar a um desequilíbrio da microbiota e, consequentemente, a infeções recorrentes.

Aconselhei a toma de um suplemento designado por **Symbiosys® Cystalia** (*SYMBIOSYS Cystalia para o equilíbrio do trato urinário - Symbiosys*, [s.d.]), que é um probiótico composto por estirpes bacterianas como *Lactobacillus rhamnosus LR06* e *Lactobacillus plantarum LP02*, que contribuem para o equilíbrio do trato urinário e inibem a proliferação de microorganismos patogénicos. Além disso, contém arando vermelho (Pina *et al.*, 2011), que é responsável pela inibição da aderência bacteriana, evitando a formação de biofilmes da *E.coli* e prevenindo a recidiva. A dose recomendada é de uma saqueta por dia, de manhã, e o pó é colocado diretamente na boca (sem necessidade de água), uma vez que é orodispersível. A embalagem contém 30 saquetas e o tratamento deve ser feito durante um mês.

Existem outras medidas não farmacológicas essenciais para a prevenção de infeções urinárias. Destaquei a importância da ingestão de água, uma vez que uma boa hidratação é crucial. Mencionei também a importância de uma boa higiene íntima, a utilização de roupa íntima de algodão e a não demora no ato de urinar, uma vez que o aumento do tempo de retenção da urina na bexiga contribui para infeções.

Caso Clínico II

Um utente do sexo masculino, idoso, dirigiu-se à farmácia com uma tosse muito intensa, afirmando ter "algo no peito que não saía", o que lhe provocava uma ligeira falta de ar. Começou a ter estes sintomas há cerca de 2 a 3 dias. No entanto, referiu que a tosse, por vezes, não parecia estar associada a expetoração. Questionei se tinha algum outro sintoma relacionado com constipação, como febre ou congestão nasal, ao qual negou. Após questionar sobre a sua medicação regular e comorbilidades, constatei que tomava medicação anti-hipertensiva.

A tosse é um reflexo/mecanismo de defesa do nosso corpo, que tem como objetivo a expulsão do agente irritante das vias respiratórias. O tratamento da tosse depende do tipo de tosse presente. Existem dois tipos de tosse: tosse seca e irritativa (não produtiva) e tosse produtiva, em que há produção de muco ou expectoração. Na tosse seca, não há produção de muco e, normalmente, resulta de ou inflamação das vias respiratórias. No caso da tosse produtiva, o reflexo da tosse é provocado pelo muco ou fluido presente nas vias aéreas.

Visto tratar-se de um idoso, com hipertensão controlada através de uma terapêutica anti-hipertensiva, aconselhei o **Bronchodual® Solução Oral** (*Bronchodual® Solução Oral | Bronchodual - Alivia qualquer Tosse*, [s.d.]), uma vez que é um medicamento tradicional à base de plantas e apresenta maior segurança nesta situação. Este medicamento tem na sua constituição dois extratos fundamentais: extrato de tomilho (*Thymus vulgaris*), com ação expetorante, facilitanto a remoção do muco, e extrato de alteia (*Althaea officinalis*), com ação demulcente/emoliente que diminui a irritação existente.

Recomendei a toma de 15mL (correspondente a uma colher de sopa) até 4 vezes por dia, no máximo durante 5 dias, e salientei a necessidade de ingestão de líquidos. É fundamental uma boa hidratação, uma vez que esta ajuda a fluidificar o muco e facilita a sua expulsão, bem como suaviza e acalma as vias respiratórias. Caso a tosse persistisse ou surgisse febre, aconselhei a ida ao médico.

Caso Clínico III

Uma utente do sexo feminino, com cerca de 25 anos, dirigiu-se à farmácia, queixando-se de sintomas característicos de uma candidíase vaginal: prurido vaginal persistente, ardor e sensação de dor. Também mencionou dor ao urinar (disúria). Questionei-a sobre o seu corrimento, a qual o caracterizou como "branco e espesso", corroborando com a hipótese de candidíase vaginal.

A candidíase vaginal (CVV) é uma infeção vulvovaginal causada por um fungo do género *Candida*, sendo o mais comum denominado por *Candida albicans*. Embora esse fungo esteja presente em quantidades baixas na flora vaginal da mulher, de forma assintomática e saudável, existem diversas situações que podem desencadear uma infeção por este fungo, levando a uma proliferação excessiva e penetração nas células epiteliais superficiais. O tratamento consiste na utilização de antifúngicos azólicos. Sendo este um caso esporádico da utente, com sintomas ligeiros, aconselhei o uso do **Candiset 3 dias®** (*Sintomas e Tratamento Candidíase Vaginal • Candiset 3 Dias®*, 2020), que é um creme vaginal contendo 20mg/g de clotrimazol (antifúngico), com a vantagem de ter um curto período de tratamento. Recomendei a sua aplicação ao deitar, por via vaginal, durante 3 dias consecutivos. Expliquei que a embalagem continha um aplicador e que deveria ser usado caso sentisse estes sintomas mais internamente. Aconselhei a utente a consultar o médico caso os sintomas persistissem após o tratamento.

No final, mencionei algumas medidas que a utente deve adotar de forma a prevenir futuras infeções por esse fungo: secar bem a área genital, evitando a humidade; utilizar roupa intíma de algodão e evitar utilizar roupa muito apertada; manter uma higiene íntima adequada, evitando produtos que possam causar irritação na área vulvar; reduzir o consumo de alimentos e bebidas com açúcar.

Caso Clínico IV

Um utente do sexo masculino, com 71 anos, dirigiu-se à farmácia com queixas de "feridas" nas mãos, especialmente nos dedos. Referiu sentir dor e uma comichão intensa quando expostas ao calor, e os dedos aparentavam estar ligeiramente inchados. Ao observar as mãos do senhor, verifiquei que se tratavam de frieiras.

As frieiras são lesões cutâneas (inflamações) que surgem após exposições climáticas extremas (frio ou calor), afetando sobretudo as extremidades do corpo, como é o caso deste senhor. Na superfície da pele, existem pequenos vasos sanguíneos superficiais que, com temperaturas mais baixas, contraem, prejudicando a circulação sanguínea nessas áreas. Para

aliviar estes sintomas, aconselhei a utilização do creme **Akilhiver®** (*Akilhiver Creme | Akileine*, [s.d.]), que atua tanto no tratamento como na prevenção de frieiras e gretas. Na sua composição, apresenta *Ginkgo biloba*, que possui propriedades antioxidantes e uma ação vasodilatadora que contribui para uma melhor circulação sanguínea e redução do inchaço (anti-edematoso). Contém também substâncias hidratantes, suavizantes e reparadoras da pele, como calêndula e manteiga de karité, que ajudam a restaurar o filme hidrolipídico natural da pele. Possui alantoína, com propriedades anti-inflamatórias, que ajuda na redução da inflamação, e diversas vitaminas, como a vitamina A e R, com propriedades regeneradoras.

Em suma, este creme de rápida absorção auxilia na proteção e resistência da pele contra o frio e, simultaneamente, hidrata e alivia as sensações de desconforto características das frieiras. De forma a prevenir futuras frieiras, aconselhei alguns cuidados a ter, tais como hidratar bem a pele, evitar mudanças bruscas de temperatura, beber muita água e adotar uma alimentação saudável, evitando alimentos que possam potenciar a inflamação.

Caso Clínico V

Uma utente do sexo feminino dirigiu-se à farmácia à procura de um creme para a muda da fralda, queixando-se que o seu filho de 9 meses apresentava o rabinho muito vermelho e irritado. Questionei-lhe se notava a presença de "pontinhos brancos", que são um sinal de infeção causada pelo fungo do tipo *Candida*, ao qual ela negou.

A dermatite da fralda é uma inflamação ou irritação da pele muito comum nos bebés, que ocorre quando a urina e as fezes permanecem em contacto prolongado com a pele, quando a pele do bebé é muito sensível ou quando existe uma reação alérgica à fralda, entre outras razões. Nestes casos, a zona genital e glútea apresentam uma vermelhidão ou eritema, podendo estender-se até à região da virilha.

Aconselhei a pomada regeneradora para a muda da fralda da **ISDIN, Nutraisdin®** (Baby Naturals) (*babynaturals Restoring nappy ointment*, [s.d.]), que é composta por óxido de zinco, um componente essencial para a proteção da pele do rabinho e promover a regeneração da barreira cutânea. Além disto, a sua fórmula contém ingredientes hidratantes e regeneradores, proporcionando uma boa hidratação da pele do bebé. Expliquei o modo de utilização: deve ser aplicada suavemente em pele seca e limpa, em camada fina, a cada troca de fralda.

Acrescentei alguns cuidados extra para prevenir futuras assaduras e promover uma melhor regeneração da pele: evitar o uso de toalhitas (com exceção das que não contêm

álcool), uma vez que podem secar a pele do bebé; a cada muda de fralda, limpar suavemente a pele do bebé com um disco de algodão embebido em água de limpeza ou água morna; não apertar demasiado a fralda; e, especificamente neste caso, sugeri que deixasse o bebé andar sem fralda durante curtos períodos de tempo, para que a pele fique exposta ao ar e acelere a regeneração. Se a dermatite se prolongasse por mais de 3 dias ou se agravasse, sugeri que entrasse em contacto com o pediatra.

5. CONSIDERAÇÕES FINAIS

O farmacêutico, como profissional de saúde, tem como objetivo principal garantir o bem-estar do utente, assegurando também a segurança na utilização do medicamento. A responsabilidade de oferecer um aconselhamento adequado e orientar corretamente o utente no seu tratamento mostra a importância do farmacêutico na área da saúde. Além disso, a partir do primeiro momento de atendimento, é estabelecida uma relação de confiança com a pessoa, tornando o atendimento individualizado e personalizado.

Após estes meses de estágio na FGC, ganhei outra perceção do que é realmente ser farmacêutico, uma perceção mais real. Na faculdade, adquirimos conhecimentos teóricos, enquanto que no estágio crescemos tanto a nível profissional, estando constantemente a aprender, como a nível pessoal. Aprender a lidar com momentos de vulnerabilidade dos utentes, lidar com diferentes situações e ter de dar uma resposta rápida mostrou-me o quão importante é sermos empáticos e pacientes na profissão farmacêutica. Foi uma experiência desafiante e gratificante do início ao fim, que me fez perceber que a profissão farmacêutica requer uma atualização constante no campo do medicamento e de novos tratamentos, de forma a prestar o melhor serviço ao utente.

Um especial agradecimento à equipa da FGC que, para além de me proporcionar uma grande oportunidade de aprendizagem, fez-me sentir em casa todos os dias e ganhar um carinho ainda maior por esta profissão. Sem eles, a evolução não seria tão grande. Um grande obrigada.

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PARTE II

Monografia

"Therapeutic management of alcohol addiction and underlying physiopharmacological mechanisms"

Sob orientação da Professora Doutora Sónia Santos

ABBREVIATIONS

AAI: Acute Alcohol Intoxication

ACh: Acetylcholine

ADH: Alcohol Dehydrogenase

ADH1B: Alcohol Dehydrogenase 1B

AIE: Intermittent Ethanol during Adolescence

ALDH: Aldehyde Dehydrogenase

ALDH 2: Aldehyde Dehydrogenase 2

AM: Amygdala

AMPARs: α-Amino-3-hydroxy-5-Methyl-4-isoxazolepropionic Acid Receptors

AUD: Alcohol Use Disorder

BAC: Blood Alcohol Concentration

BDNF: Brain-Derived Neurotrophic Factor

BZDs: Benzodiazepines

Ca^{2+}: Calcium

CBD: Cannabidiol

CeA: Central Nucleus of the Amygdala

ChAT: choline O-Acetyltransferase

CIE: Chronic Intermittent Ethanol

CNS: Central Nervous System

COX-2: Cyclooxygenase-2

DA: Dopamine

DCX: Doublecortin

DG: Dentate Gyrus

DTI: Diffusion Tensor Imaging

DTs: *Delirium tremens*

EMA: European Medicines Agency

EU: European Union

FAS: Fetal Alcohol Syndrome

FASD: Fetal Alcohol Spectrum Disorders

GABA: Gamma-aminobutyric Acid

$GABA_AR$: $GABA_A$ Receptors

GHB: Gamma-Hydroxybutyrate

GLT-1: Glutamate Transporter 1

GWAS: Genome-Wide Association Studies

HC: Hippocampus

iGluRs: Ionotropic Glutamate Receptors

IL-1: Interleukin-1

IL-6: Interleukin-6

INE: Instituto Nacional de Estatística

iNOS: Inducible Nitric Oxide Synthase

ISPSs: Inhibitory Postsynaptic Potentials

mGluRs: Metabotropic Glutamate Receptors

mPFC: Medial Prefrontal Cortex

MRI: Magnetic Resonance Imaging

NA: Noradrenaline

NAcc: *Nucleus Accumbens*

NMDARs: N-Methyl-D-Aspartate Receptors

NO: Nitric Oxide

NR2B-NMDAR: NMDA Receptor 2B

NSAID: Non-Steroidal Anti-Inflammatory Drug

OFC: Orbitofrontal Cortex

PFC: Prefrontal Cortex

SMO: Sodium Oxybate

SNPs: Single Nucleotide Polymorphisms

ST: Striatum

SVZ: Subventricular Zone

ThDP: Thiamine Diphosphate

TLR4: Toll-Like Receptor 4

TNF-α: Tumor Necrosis Factor

TPP: Thiamine Pyrophosphate

VTA: Ventral Tegmental Area

WHO: World Health Organization

RESUMO

A adição ao álcool tem-se tornado uma preocupação crescente em Portugal e na União Europeia, impactando significativamente a vida dos jovens. As alterações provocadas por esta substância aditiva nas diferentes áreas cerebrais, como a área tegmental ventral e o córtex pré-frontal, contribuem para os efeitos sentidos após intoxicação aguda e intoxicação crónica.

Esta revisão compila informação acerca dos mecanismos envolvidos na adição ao álcool, considerando os diferentes tipos de consumo. São reunidos estudos realizados em animais, como ratos Wistar, e em seres humanos. Também é abordada a temática do consumo alcoólico na adolescência e da consequente dependência, bem como as suas implicações futuras. Os estudos apresentados demonstram as alterações estruturais e funcionais decorrentes do consumo excessivo na adolescência, uma fase em que o cérebro se encontra em desenvolvimento. A perda abrupta da substância cinzenta cerebral e o desenvolvimento retardado da substância branca cerebral são considerados responsáveis por comportamentos impulsivos e uma maior probabilidade de envolvimento em comportamentos de risco após exposição ao álcool na adolescência.

Por fim, esta revisão incide nas diferentes intervenções, tanto farmacológicas como não farmacológicas, para tratar a dependência alcoólica, distinguindo as estratégias utilizadas na intoxicação aguda e crónica. Novas moléculas estão em desenvolvimento com o objetivo marde encontrar a terapêutica mais adequada para cada indivíduo, uma vez que o tratamento deve ser personalizado de acordo com as características de cada pessoa. Para uma melhor compreensão dos diferentes mecanismos de ação do álcool e da sua adição, é necessária a realização de mais estudos, uma vez que certas informações provenientes de pesquisas são contraditórias.

Palavras-chave: Adição, Álcool, Intoxicação aguda, Intoxicação Crónica, Adolescência, Intervenções farmacológicas, Intervenções não farmacológicas.

ABSTRACT

The addiction to alcohol has become a growing concern in Portugal and European Union, significantly affecting the lives of young people. The changes caused by this addictive substance in different brain areas, such as the ventral tegmental area (VTA) and the prefrontal cortex (PFC), contribute to the effects experienced after acute and chronic intoxication.

This review compiles information about the mechanisms involved in alcohol addiction, considering different types of consumption. Studies conducted in animals, such as Wistar rats, and in humans are gathered. The theme of alcohol consumption and its consequent dependence in adolescence, as well as its future implications, are also addressed. The presented studies demonstrate the structural and functional alterations resulting from excessive consumption during adolescence, a phase when the brain is still developing. The abrupt loss of grey matter and the delayed development of white matter in the brain are considered responsible for impulsive behaviours and a higher likelihood of engaging in risky behaviours after alcohol exposure in adolescence.

Finally, this review focuses on different interventions available, both pharmacological and non-pharmacological, for treating alcohol dependence, distinguishing the strategies used for acute and chronic intoxication. New molecules are being developed with the aim of finding the most suitable therapy for each individual, as treatment should be personalized according to individual characteristics. To a better understanding of the different mechanisms of alcohol and its addiction, further studies are necessary, as certain research findings may be contradictory.

Keywords: Addiction, Alcohol, Acute Intoxication, Chronic Intoxication, Adolescence, Pharmacological Interventions, Non-pharmacological Interventions.

1. INTRODUCTION

Addiction is a chronic disease of the Central Nervous System (CNS), often complex and misunderstood, that involves various factors and affects people's lives in different ways. It compromises a series of brain circuits and structures (mesencephalic, limbic and cortical) involved in the brain reward system. This disorder can arise at any stage of life and encompass various substances or situations, such as addictive drugs, alcohol, gambling, or even work. It is characterized by an intense desire to consume the addictive substance, with loss of control, even with the awareness of the consequences that its continued use will bring; the obsession with the addictive substance and its acquisition is also characteristic of this disorder.

As mentioned, drugs of abuse and other substances such as alcohol, despite having different mechanisms of action, converge in the same circuit – **the brain reward system**. This system is responsible for processing information related to the sensation of reward or pleasure, and it involves the release of dopamine. Since these pleasurable experiences lead to the release of this neurotransmitter, the more frequent they are the higher the difficulty in fighting this addictive behaviour. In fact, the greater the reinforcing effect of the substance (meaning the sensation of reward and pleasure through its consumption) the greater the craving (powerful desire) felt subsequently. A theory called the "incentive salience theory of addiction was proposed in 1993 by Terry Robinson and Kent Berridge. According to this theory, after being exposed to a rewarding stimulus, the mesolimbic systems in the brain generate a sense of "incentive salience" (Robinson e Berridge, 1993). This refers to the motivational behaviour that drives the intense pursuit of these rewarding substances. Drugs of abuse and alcohol can enhance the significance of cues associated with their use, which explains the strong desire experienced after consuming them. Generally, three components are necessary to create a sensation of reward: "liking", "predictive learning", and "wanting". As a result, alcohol and drugs of abuse, due to their incentive salience, acquire a motivational value that leads to their consumption because they are "wanted" rather than solely being "liked" for their pleasurable effects (hedonic value) (Berridge, 2007).

The addictive disorder is understood as brain changes that are influenced by a set of factors, including genetic, environmental, and behavioural factors. An example of this is the post-consumption of alcohol genetic predisposition within a family – brain changes that lead to the development of later problematic alcohol use in people with a family history of alcoholism. Stress, trauma, anxiety, or depression are other factors that play a significant role in the development of this disorder.

The characteristic underdevelopment of the brain during adolescence, impulsivity, and decreased inhibitory control may explain the high probability of entering into addictions during this stage, as well as the undervaluation of the negative impacts they have on mental health, emotions, and relationships.

The present review focuses on alcohol addiction, its impact on adolescents, and the consequences in adulthood related to early alcohol exposure. It is known that, during adolescence, the brain is still developing and maturing, which is why this period is critical, and it is increasingly important to alert this generation to the dangers of alcohol and the repercussions that its exposure can bring. Management strategies, both for acute and chronic consumption, will also be discussed.

2. ALCOHOL ADDICTION

2.1 ALCOHOL CONSUMPTION EPIDEMIOLOGY AND ITS PATTERNS

There are different patterns of alcohol consumption, each accompanied by its respective risks and consequences. Naturally, the greater the intensity and frequency of consumption, the more severe the resulting consequences will be. We can identify moderate drinking, binge drinking, and heavy drinking as the main patterns. Depending on the survey conducted and the institution, binge drinking can be defined as consuming 4 or more alcoholic beverages for women or 6 or more for men on the same occasion. It is also considered binge drinking if, on a single occasion, there is a consumption of 40g of pure alcohol for women and 60g for men. Binge drinking describes consumption on a particular day or moment, while heavy drinking describes consumption over time, specifically on a weekly basis. Heavy drinking is defined as consuming 8 or more alcoholic beverages per week for women and 15 or more for men. Different surveys describe the state of intoxication as being unsteady, experiencing difficulties in speech, and having momentary memory lapses (*What is excessive alcohol use?*, 2019).

According to the Instituto Nacional de Estatística (INE, IP), in 2020, in Portugal, 2544 deaths were attributed to alcohol-related causes (similar to the 2019 period, which was the highest in the last decade). Additionally, there was an increase in hospitalizations in 2021 (a rise of 14% in mainland Portugal) following a decline in 2020 (*Relatório Anual 2021 • A Situação do País Em Matéria de Álcool*, [s.d.]). The Annual Survey "Comportamentos Aditivos aos 18 anos- Inquérito aos jovens participantes no Dia da Defesa Nacional de 2021"(*SICAD*, [s.d.]) revealed a stable prevalence of high alcohol consumption compared to the 2018-2019 period,

but slightly higher than in 2015 and 2017. Moreover, there has been a significant increase in the occurrence of alcohol-related problems.

According to the 2019 "Status Report on Alcohol Consumption" presented by the World Health Organization (WHO) (World Health Organization. Regional Office for Europe, 2019), alcohol consumption, in the European Union (EU), did not undergo significant changes between 2010 and 2016, but the associated burden and problems escalated considerably. Furthermore, in 2016, within the EU, 291000 deaths were deemed preventable, highlighting alcohol as one of the primary risk factors for mortality and morbidity.

2.2 ALCOHOL'S PATHOPHYSIOLOGY

2.2.1 Brain Reward System and its components

The brain reward system is a complex neuronal circuit responsible for the processing of pleasurable experiences and the reinforcement of behaviours essential for survival (such as eating, drinking, and reproduction). It plays a crucial role in motivation and reward processing. This system responds to both natural positive stimuli (such as food, water, and sexual activity) and psychoactive substances (drugs of abuse), although these substances create a different and more tempting effect, leading to an obsessive behaviour and an intense desire for consumption (accompanied by difficulty in controlling the desire) (Kelley e Berridge, 2002; Nestler, 2005).

This complex circuit is composed of structures that are associated with the mesolimbic dopaminergic system and several other brain regions. It is known that the brain has two major dopamine (DA) systems: the nigrostriatal dopaminergic system (originating in the *substantia nigra pars compacta* with projections in the striatum, caudate, and putamen), and the mesocorticolimbic dopaminergic system [originating in the Ventral Tegmental Area (VTA with projection in the Nucleus Accumbens (NAcc) and prefrontal cortex (PFC)) (Martin, 2021). In different studies, the mesolimbic dopamine pathway appears to be of greater importance and relevance to addiction and addictive behaviours caused by drugs of abuse, and that is what we will focus on.

The primary components of the brain reward system include the VTA, NAcc, PFC, Amygdala, and Hippocampus (Nestler, 2005).

The mesocorticolimbic dopaminergic system involves projections that originate from the VTA, which are neurons located in the midbrain, and extend to various regions of the brain, with the NAcc being one of the main targets (Martin, 2021). The NAcc is a region located in the basal forebrain and plays an important role in addiction and the reinforcing

effects of substances of abuse. Microdialysis studies conducted in rats have shown that the administration of drugs of abuse leads to an increase in extracellular DA, especially in the NAcc (Carboni *et al.*, 1989). Later, using the same methods, it was demonstrated that non-human primates (Rhesus monkeys) also experienced a similar increase in dopamine levels in this particular brain area (Bradberry *et al.*, 2000). Additionally, the DA signals from the VTA-NAcc pathway are involved in the processing and integration of rewarding stimuli. In other words, the phasic activation of dopaminergic neurons by drugs of abuse, such as alcohol, leads to the formation of associations between drug-related events and rewarding experiences, contributing to impulsive and compulsive substance abuse. Once the dopaminergic system becomes sensitized, the desire for consumption increases exponentially, as the sense of reward is not easily achieved as it was in the beginning (Wise, 2004). Certain evidence demonstrates that certain drugs of abuse can provoke cross-tolerance and cross-sensitization with each other. This means that when an individual becomes sensitized to a specific drug, they may also develop sensitized effects when exposed to other different drugs. It has also been proven that non-drug-related stress (in other words, exposure to stressors that are not related to drugs) can lead to sensitization to drugs of abuse (Robinson e Berridge, 2003).

In addition to the NAcc, the mesolimbic system ensures the main neuronal transmission of DA to the amygdala, hippocampus, and various parts of the cortex, especially the PFC. The amygdala is an almond-shaped structure divided into three major nuclear parts, all involved in the processing of emotions and emotional memories. The division most related to reward and addiction is the central nuclei. The amygdala system can regulate the reinforcing effects of addictive substances, the neuroadaptations involved in chronic consumption, and is particularly relevant in the associations formed between rewards and emotional responses, as well as in their consolidation (it aids in assigning emotional meaning to rewarding/positive stimuli) (Martin, 2021). The hippocampus is involved in learning and memory processes. In the brain reward system, dopaminergic projections into the hippocampus are responsible for the formation and retrieval of memories associated with rewarding experiences. This region stores memories related to rewards and pleasure-associated experiences, which can influence future decision-making and behaviours of the individual – addiction involves intense emotional memories (Tyng *et al.*, 2017). Last, but not least, we have regions of the cortex, such as the PFC, which are crucial in decision-making, impulse control, and evaluating rewards. The NAcc is part of the limbic loop (a loop that provides emotional context for planning motor behaviour) that projects into the PFC. The information received by the PFC from the NAcc

helps regulate the activity of the brain reward system and guides people's behaviour by evaluating the value and possible consequences of rewards (Martin, 2021).

There is evidence that the mesocorticolimbic dopaminergic system is activated not only by positive stimuli but also by aversive stimuli. In a study conducted on male humans, different painful stimulus activated several brain areas, such as the NAcc and the PFC (Becerra *et al.*, 2001). In conclusion, this dopaminergic system and the release of DA from the VTA to the NAcc, along with communication with other regions of the brain, regulate human behaviour and guide decision-making based on past experiences and acquired memories. Dysfunctions in the brain reward system can lead to various psychiatric disorders, such as addiction, depression, and schizophrenia.

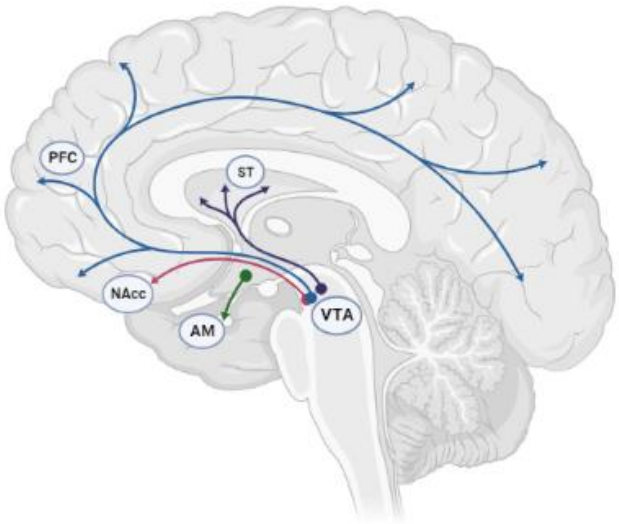

***Figure 1*. Dopamine projections in the human brain, which are part of the brain reward system.** *Dopamine transmission originates from the VTA and extends to the NAcc, the amygdala, the striatum, and the PFC. AM: Amygdala; NAcc: Nucleus Accumbens; PFC: Prefrontal Cortex; ST: Striatum; VTA: Ventral Tegmental Area. [Created with BioRender.com]*

2.2.2 Mechanism of alcohol addiction

Alcohol addiction is a complex disorder, still with unknown processes and mechanisms, and with certain contradictory evidence. It is certain that alcohol, being considered a drug of abuse, will cause alterations in the brain reward system and, consequently, modifications in the human body and behaviour. Although the precise causes of alcohol addiction are not fully understood, there are certain factors that contribute to its development, and the changes caused by this substance in neurotransmitters, such as gamma-aminobutyric acid (GABA), dopamine, glutamate, and serotonin, are one of them.

With chronic alcohol consumption, there is an increase in DA release in various brain areas belonging to the mesocorticolimbic dopaminergic system. Similar to natural rewards,

drugs of abuse have rewarding effects by acting on the brain reward system, leading to excessive and repeated consumption associated with loss of control. Several studies have shown that after alcohol consumption, dopaminergic transmission in the VTA sharply increases due to disinhibition of ventral tegmental neurons, resulting in a subsequent increase in DA release in the NAcc through the VTA-NAcc pathway (Bradberry *et al.*, 2000; Carboni *et al.*, 1989; Martin, 2021). Additionally, there are mechanisms that decrease dopamine reuptake in the synapses (resulting in an increase in synaptic DA content), contributing to a powerful reinforcing effect (Wise e Robble, 2020). Similar to positive stimuli (explained in point 2.2.1), continuous exposure to alcohol is associated with dopaminergic transmission directed to the amygdala, PFC, and hippocampus, favouring the vicious and impulsive behaviour involved in alcohol dependence.

With frequent alcohol consumption, the body tries to adapt to the constant activation of the dopaminergic system and generates a "homeostatic response", or in other terms, develops tolerance. This means that to achieve the same desired and rewarding effects, a higher amount of alcohol is required. With decreased baseline levels of dopamine, stimulation with "normal" levels of alcohol becomes insufficient and leads to negative symptoms associated with withdrawal, such as tremors and anxiety (Robinson e Berridge, 2003). On the opposite side we can have sensitization of the dopamine system, which is a mechanism responsible for an enhanced response of the brain's dopamine pathways to subsequent alcohol exposure. The dopamine receptors become more sensitive and have a greater capacity to respond, thus amplifying the response obtained from alcohol consumption. This supports the idea that with frequent and more intense exposure to this addictive substance, cravings will be stronger, as dopamine release keeps increasing, which can trigger relapses even after a period of abstinence (Robinson e Berridge, 2003).

In addition to dopamine, alcohol also interacts with GABA and glutamate circuits. In acute consumption, by promoting the function of $GABA_A$ receptors ($GABA_AR$), it potentiates GABAergic terminals in the VTA and simultaneously acts on dopaminergic neurons as mentioned above (Melis *et al.*, 2002; Rao *et al.*, 2015; Theile *et al.*, 2008). It also has significant effects on glutamate and its receptors, reducing glutamatergic activity by inhibiting glutamatergic terminals that innervate NAcc neurons. Furthermore, certain studies have shown that alcohol (similarly to opioids) can activate endogenous cannabinoid pathways (acting on the endocannabinoid receptor-1 in hippocampal neurons) and inhibit the release and transmission of glutamate by neurons (Basavarajappa, Ninan e Arancio, 2008). The mechanism of chronic consumption is the opposite of acute consumption.

The glutamatergic projection system is also involved in the mesocorticolimbic pathway, participating in the known mechanisms of alcohol addiction. This system interacts with the same brain regions that dopamine interacts with, but through different pathways (Kalivas *et al.*, 2009). Drug-seeking behaviours originate from the arrival of glutamate in the NAcc from other brain regions related to the reward system. One of the key projections involved in initiating alcohol consumption and driving its dependence is the glutamatergic projection that originates from the PFC and targets the NAcc. Glutamatergic projections from the amygdala and hippocampus to the NAcc and PFC plays a significant role in the associations formed between stimulus reception and the formation of related memories, leading to craving. The hippocampus, crucial for memory function, also delivers glutamate to the NAcc and PFC, further contributing to the persistent desire for alcohol associated with reward-related emotions (Martin, 2021).

A study conducted on Wistar rats, where they were exposed to alcohol for 4 consecutive days (intoxication days) followed by 3 days of recovery (no alcohol exposure), demonstrated a clear increase in extracellular glutamate levels in the NAcc during the withdrawal phase (using the microdialysis technique) (Saellstroem Baum *et al.*, 2006). This increase in glutamate concentration during withdrawal from chronic alcohol consumption is considered one of the reasons for intense cravings and a high likelihood of relapse (Griffin Iii *et al.*, 2014). Additionally, it is responsible for typical withdrawal symptoms. Further evidence has supported this hypothesis bye indicating that, after prolonged alcohol consumption, there is a reduction in the expression of glutamate transporter 1 (GLT-1), a critical transporter for glutamate uptake in various brain areas and for glutamate homeostasis. Because of decreased GLT-1 expression, the body exhibits an elevation in extracellular glutamate levels in the NAcc (also demonstrated in male rats using microdialysis) due to reduced glutamate uptake (Das *et al.*, 2015).

Glutamate, as a key mediator of synaptic plasticity, can interfere with learning and memory processes. Both acute and chronic alcohol consumption can disrupt glutamatergic signalling, which can affect the connectivity and strength of neuronal pathways and influence responses, associated memories, and addiction-related behaviours. In addition to these modification in the glutamatergic system, prolonged alcohol use leads to adaptive changes in the expression and function of glutamate receptors (presynaptic and postsynaptic) and glutamate transporters (Alasmari *et al.*, 2018).

Glutamate transporters can be divided into two categories: ionotropic glutamate receptors (iGluRs), associated with ion channel transport (Wyllie e Bowie, 2022), and

metabotropic glutamate receptors (mGluRs), which are coupled to G-proteins, with synaptic transmission occurring through second messengers (Niswender e Conn, 2010). There are three types of iGluRs: N-Methyl-D-Aspartate receptors (NMDARs), α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), and Kainate receptors. Regarding the expression of NMDARs, despite contradictory results, there is agreement that acute alcohol exposure leads to a decrease in the expression of these receptors, which explains the sedative effects of initial alcohol consumption, while chronic exposure results in an increase in NMDAR-mediated glutamatergic transmission and NMDAR-mediated plasticity. A study provided evidence that alcohol exposure (*ex vivo or in vivo*) is responsible for a prolonged increase in NR2B-NMDAR activity in the dorsal striatum (DS), favouring and promoting continued substance consumption (Chen *et al.*, 2011). To confirm the influence of the NR2B subunit of these ionotropic receptors on excessive alcohol consumption, the study showed that ifenprodil, a selective NR2B-NMDAR antagonist, led to a decrease in ethanol levels and its consumption. In rats, repeated alcohol exposure contributes to an increase in the expression and synaptic localization of AMPARs, enhancing glutamatergic transmission and subsequently, the rewarding effects experienced during and after ingestion (amplified drug-seeking behaviours)(Goodwani *et al.*, 2017; WANG, Jun *et al.*,2012).

Regarding mGluRs, they can be divided into three groups with different functions and locations: Group I mGluRs (mGluR1, mGluR5) responsible for slow excitatory effects and associated to phospholipase C signalling pathway, Group II mGluRs (mGluR2, mGluR3), and Group III mGluRs (mGluR4, mGluR5, mGluR6, mGluR7, mGluR8), both responsible for slow inhibitory effects and associated negatively to adenylcyclase. A study conducted on male Wistar rats showed a decrease in the transcription of the mGluR2 gene and a subsequent decrease in the expression of this receptor after excessive alcohol consumption. Since mGluR2 acts as an autoreceptor, this will contribute to an increase of glutamatergic neurons firing and an increased risk of relapse (after a period of abstinence) (Meinhardt *et al.*, 2013). Additionally, it was observed that replenishing the levels of mGluR2 in the infralimbic cortex nullified the previously observed effects, and the heightened reinstatement response to alcohol was reversed. In contrast to this group, an upregulation of mGluR1 expression was identified in Group I of mGluRs after continuous alcohol consumption, indicating that mGluR1 antagonists may be a possible alternative to treat alcohol disorder (Goodwani *et al.*, 2017).

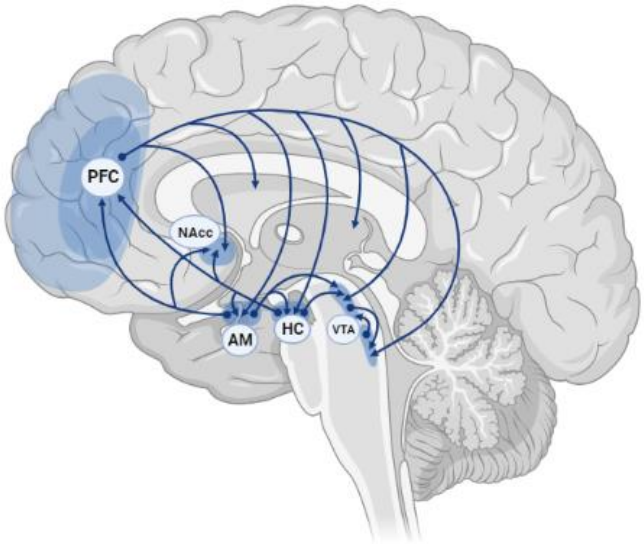

Figure 2. Glutamatergic projections in the human brain, responsible for drug seeking behaviours and relapse. *AM: Amygdala; HC: Hippocampus; NAcc: Nucleus Accumbens; PFC: Prefrontal Cortex; VTA: Ventral Tegmental Area. [Created with BioRender.com]*

2.3 ACUTE PHYSIOPATHOLOGY VS. CHRONIC PHYSIOPATHOLOGY

The effects on the Central Nervous System (CNS) will depend on the type of alcohol intoxication – acute or chronic intoxication.

Acute intoxication by alcohol refers to a short-term effect that occurs when a person consumes a large amount of alcohol within a short period of time. This can lead to several symptoms and disturbances such as slurred speech, impaired judgment, impairment of memory or attention, loss of coordination, nystagmus, and potentially dangerous behaviour. In extreme cases, acute alcohol intoxication can lead to alcohol poisoning, which can be life-threatening. In young people, since liver enzymes are not fully developed and alcohol metabolism is inadequate, this pattern of consumption is extremely dangerous. Moreover, especially at these ages, alcohol consumption never occurs in isolation and is often associated with the use of drugs and other addictive and harmful substances (Mirijello *et al.*, 2023).

In excessive amounts, alcohol leads to a series of physiological and behavioural effects, as it functions as a depressant substance of the CNS, causing the brain, neurons, and the body in general to act slowly (Pereiro Gómez, 2010). Although not fully understood, the mechanism of action of alcohol is based on its interaction with different neurotransmitters, including DA, glutamate, and GABA as described before. Acute administration causes an increase in the inhibitory activity of GABA and a decrease in the excitatory activity of glutamate, calcium channels (Ca^{2+}), and noradrenaline (NA) (namely through a reduction in the activity of NMDA and AMPA/Kainate receptors) (Bensmann *et al.*, 2020). With the dysregulation of the levels of these neurotransmitters, we have CNS depression, with a reduction in neuronal activity and

consequent sedative and anxiolytic effects. In addition, alcohol influences DA levels in the synapses of the ventral striatum (NAcc), contributing to the euphoric state and reinforcement.

Chronic alcohol intoxication, on the other hand, refers to the long-term effects of alcohol consumption over an extended period of time. Chronic alcohol abuse can lead to overall neurological impairment, as well as a range of physical and mental health problems, including liver disease, heart disease, gastrointestinal problems, depression, coma and cardiorespiratory arrest. Chronic alcoholism can also lead to social, occupational, and legal problems.

In chronic alcohol consumption, the body will attempt to compensate for the changes caused by ethanol through compensatory neuroadaptive changes. Therefore, it would be expected that chronic consumption would lead to a reduction in GABA receptor activity and an increase in glutamate receptor activity – glutamatergic and noradrenergic hyperfunction, as well as calcium channel hyperfunction, and GABAergic hypofunction. Due to the complexity of these interactions, certain studies are contradictory, making this area of knowledge a vast field for future discoveries and certainty.

GABA receptors can be both presynaptic and postsynaptic and are divided into 5 subunits, each with different isoforms that determine specific properties depending on their location. An *in vitro* (Roberto *et al.*, 2004) study using amygdala slices from rats (Sprague Dawley) with a control group – Naive rats – and a study group – rats subjected to chronic alcohol consumption treatment – allowed the evaluation of GABA release after acute and chronic consumption of this substance. Using neurons from the central nucleus of the amygdala (CeA) and with the aid of electrical stimulation techniques to measure GABA inhibitory postsynaptic potentials (ISPSs), it was observed that both acute and chronic exposure to ethanol lead to GABAergic hyperfunction, with an increase in GABA release and transmission in the CeA. Another study conducted in rats subjected to the chronic intermittent ethanol (CIE) model (alternating periods of alcohol intoxication and withdrawal) revealed increases in the expression of certain subunits of GABA receptors, such as α_4 and γ_2, and a decrease in α_1 and δ in the hippocampus (Cagetti *et al.*, 2003). These changes may be one of the justifications for the development of alcohol tolerance. Although controversial, it is suggested that initially, during chronic drinking, these aforementioned changes occur, but over time, there may be a gradual decrease in the activity and number of GABA receptors (Davis e Wu, [s.d.]).

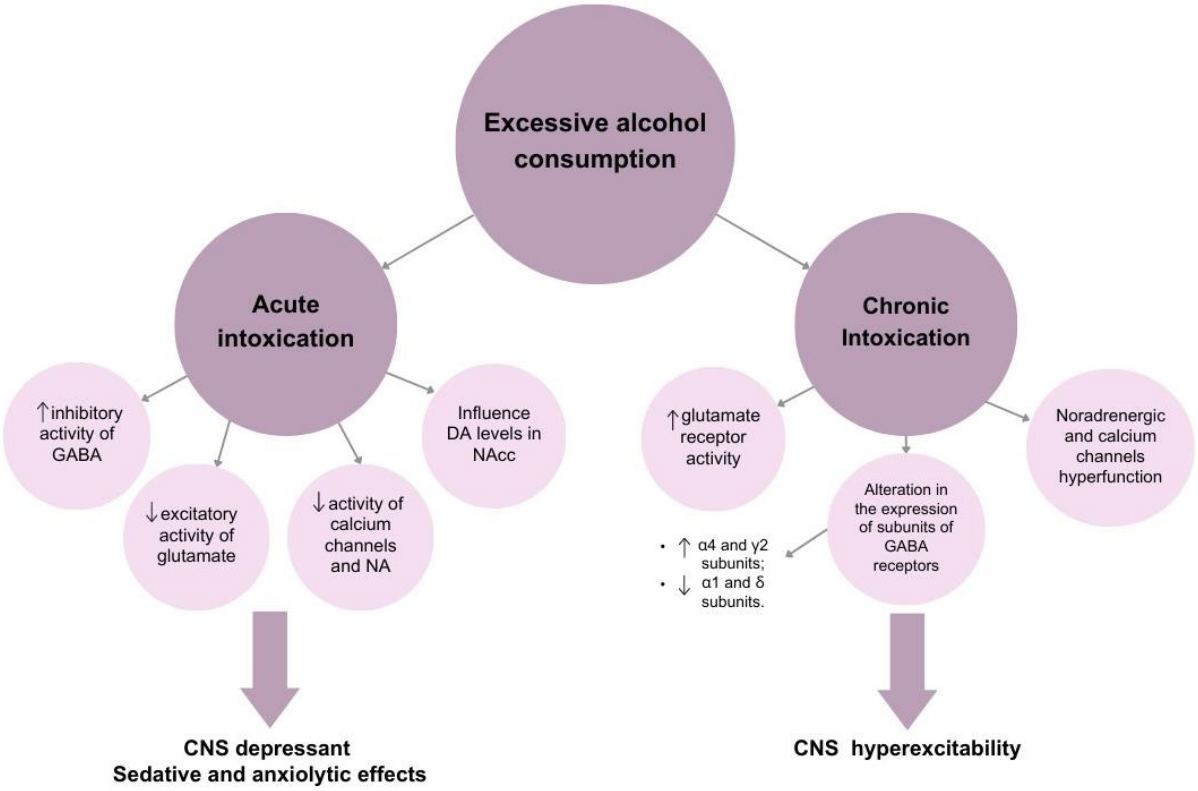

Figure 3. Alcohol Consumption: Acute vs. Chronic Effects*. DA: dopamine; NA: noradrenaline; NAcc: nucleus accumbens; CNS: central nervous system.*

Due to these compensations, when a person abruptly stops drinking, withdrawal symptoms begin to manifest, which are a result of the brain seeking chemical balance. Symptoms of tolerance, craving and impulsivity also begin to manifest, with a decline in behavioural self-control, which increases the likelihood of relapse due to the intense desire to consume alcohol.

The type and severity of the abstinence symptoms can vary depending on the length and intensity of alcohol consumption and they vary depending on the time/days without consuming. Withdrawal symptoms can be dangerous, especially in cases of severe alcohol use, and should be monitored by a medical professional. Within the first 24 hours, a person may experience signs of anxiety, restlessness, tremors, tachycardia, and hypertension. Between 58-72 hours after stopping drinking, there may be marked restlessness, nausea, vomiting, and diarrhoea, along with generalized convulsive seizures and mild confusion. From 72-96 hours of abstinence, *delirium tremens* may begin to appear, with fever, tachycardia, hypertension, and hallucinations (Mirijello *et al.*, 2023; Ropper *et al.*, 2023). This underscores how essential it is to have the supervision of a healthcare professional to ensure that a person safely overcomes these withdrawal symptoms in the most comfortable way possible since abstinence can lead to potentially life-threatening complications, even death.

Alcohol abuse and dependence can generate various neuropsychiatric complications associated with its consumption, such as psychotic disorders – transient hallucinations, alcoholic hallucinosis, and jealousy delusion – behavioural disorders, and neurocognitive disorders – *delirium tremens*, Wernicke-Korsakoff syndrome, cognitive deterioration/dementia, and fetal alcohol syndrome (Mirijello *et al.*, 2023; Ropper *et al.*, 2023). Furthermore, this can lead to depression and later, suicide. Some of these neuropsychiatric complications are described in box 1.

Table 1. Neuropsychiatric complications associated with alcohol abuse and dependence.

Wernicke- Korsakoff Syndrome
This syndrome is the combination of Wernicke encephalopathy (an acute neurological condition characterized by a clinical triad of ophthalmoplegia, ataxia, and confusion) and Korsakoff syndrome (a chronic memory disorder). It is a neurological disorder that results from a severe deficiency of thiamine in the brain, an important nutrient in the metabolism of carbohydrates into glucose. Thiamine, also known as vitamin B1, is an essential cofactor in various metabolic processes of the body. Its mechanism involves conversion into its active form, thiamine pyrophosphate (TPP) or thiamine diphosphate (ThDP). This form serves as a cofactor for several enzymes involved in chemical bond formation, including those in the Krebs cycle and other pathways, such as α-ketoglutarate dehydrogenase (Frank, Leeper e Luisi, 2007). Without thiamine, the body does not have enough energy and presents symptoms such as fatigue, dizziness, memory loss, and tachycardia. Since alcohol interferes with the intestinal absorption of thiamine, this deficiency is most commonly related to chronic alcoholism but can also occur in people with other thiamine deficiency disorders (Wijnia, 2022).
Delirium Tremens ("DTs")
Is characterized by a combination of physical and psychological symptoms that include profound confusion, hallucinations (usually visual and vivid), seizures, delusions, tremors, and others. Additionally, there is an increase in the activity of the autonomic nervous system, manifested through high fever, accelerated heartbeats (tachycardia), heavy sweating (hyperhidrosis), and dilated pupils. This is a severe and potentially fatal form of alcohol withdrawal that usually occurs in individuals who have a history of heavy alcohol use (Ropper *et al.*, 2023).
Fetal Alcohol Syndrome (FAS)
Is the most severe syndrome of FetaL Alcohol Spectrum Disorders (FASD). This is a congenital condition caused by the consumption of alcohol during pregnancy, as alcohol quickly crosses the human placenta and damages the fetus's brain and organs. After

exposure to alcohol, children experience a range of behavioural, physical, and cognitive impairments, such as smaller head size, growth deficiencies (shorter-than-average height), vision/hearing disorders, intellectual disabilities, hyperactive behaviour, and so forth. This can be prevented by avoiding alcohol exposure during pregnancy, regardless of the month or trimester (Wilhoit, Scott e Simecka, 2017).

Alcoholic Hallucinosis

Different from *delirium tremens*, this is a type of alcohol withdrawal syndrome characterized by vivid hallucinations, usually of an auditory nature (with human voices being the most common hallucinations). The person has difficulty separating the hallucinations/visions from reality, leading to significant paranoia and anxiety. Its duration varies significantly (can last for hours, days, and in exceptional cases weeks or months), and they are more intense and frequent at night (Ropper *et al.*, 2023).

3. CHARACTERISTICS OF THE ADOLESCENT BRAIN AND ITS DEVELOPMENT/MATURATION

The human brain grows rapidly during early childhood, reaching almost 90% of its adult size by the age of 6. It undergoes several changes from adolescence to adulthood, with its maturation continuing until around the age of 25. It is known through various studies that the adolescent brain has similarities to the brains of mammalian species, which has contributed to the knowledge we have today about the development of the human brain. There are changes in the levels and receptors of neurotransmitters such as GABA, DA and glutamate, which affect cognitive and emotional processes during adolescence.

The young brain has a greater capacity for neuroplasticity than the adult brain, but this decreases as the brain matures. The brain undergoes significant functional and structural changes due to environmental factors and excitatory and inhibitory stimuli in the nervous system. Thus, neuroplasticity is understood as a process of adaptation of the brain in response to different neurobiological processes, being considered one of the main bases for learning, memory and visual development (Bandeira *et al.*, 2021). The brain remains highly adaptable to new experiences during adolescence, as there is development and refinement of neural connections. At the same time, during this period, it is also in a more critical and sensitive phase to negative external factors and bad experiences (involving stress or trauma), which can cause damage to the brain and lead to several disorders later on (such as depression and schizophrenia).

With the maturation of the brain during adolescence, there is a loss of up to 50% of synapses. Our body excessively produces neuronal elements, such as neurons, and subsequently destroys those that are unnecessary, a process known as synaptic pruning. During adolescence, the brain undergoes a process of synaptic pruning where dispensable synapses are eliminated, helping to refine the neural connections that are most important for cognitive functions, such as memory and learning.

Human imaging has revealed two major changes in the adolescent brain: grey matter reductions in portions of the dorsolateral PFC and temporal lobe (which occurs in late adolescence) and white matter increases in cortical and subcortical fibber tracts. Reductions in grey matter in the striatum and other subcortical structures have also been observed. Grey matter is an outer layer of the brain, and its grey colour is due to its rich composition of neuronal cell bodies, dendrites and unmyelinated axons. Its reduction may be related to the synaptic pruning undergone during adolescence (observed in humans and primates). In Rhesus monkeys, synaptogenesis was evaluated through the performance of a quantitative electron microscopy analysis, which confirmed a significant decline in synaptic density (Bourgeois, Goldman-Rakic e Rakic, 1994). On the other hand, white matter is composed of a set of axons coated with myelin (a lipid membrane composed of lipids and proteins), which has an important function in conducting nerve impulses/signals and helps to speed up neural transmission. The increase in this layer is due to continued elaboration of myelin (myelination) and an increase in the thickness of axons, leading to more efficient communication between different regions of the brain, improved processing speed and cognitive efficiency. This maturation of the brain's grey matter was evidenced through time-lapse sequences and quantitative four-dimensional maps in children selected for a study, ranging in age from 4 to 21 years, with reassessments every 2 years (neurocognitive and psychiatric evaluations were performed in conjunction with a magnetic resonance imaging (MRI)) (Gogtay *et al.*, 2004).

Although there are different studies with varied results, there is evidence that the adolescent brain may be more sensitive to rewards than the adult brain. Neuroimaging studies have shown that, compared to adults, adolescents appear to have a reduced hemodynamic response in the lateral orbitofrontal cortex (OFC) when receiving rewards, and increased activity in the ventral striatum. The OFC is a component part of the limbic association cortex and is responsible for receiving information from all sensory modalities – thus, it plays an important role in decision-making and evaluation of the hedonic value of stimulation. The ventral striatum and other subcortical structures are involved in the brain's reward system

and related to reward-related behaviours, processing of pleasurable experiences, and decision-making.

As mentioned earlier, neurotransmitter systems also differ when compared to adults, contributing even more to sensitivity to rewards, sensation seeking, and impulsivity in actions taken (decreased inhibitory control). It has been proven that during adolescence, there are peaks in the dopaminergic system. With the activation of the mesolimbic and mesocortical dopaminergic projections during adolescence, heightened reward sensitivity to certain reward-related events is understandable. At the same time, there is evidence that adolescents have decreased inhibitory control (lower inhibitory tone in PFC) compared to adulthood, exhibiting a greater number of excitatory synapses and lower baseline levels of $GABA_AR$ in the hippocampal dentate gyrus. This contributes to the desire for new, riskier experiences and certain types of behaviours that can have negative consequences in their lives. The ratio of inhibition to excitation is lower in adolescence and tend to reverse as age increases, hence the greater stability and reflection in the decisions made as adults.

It is important to note that several studies have shown that brain development varies depending on sex, with females having an earlier brain development than males (one to two years earlier) (Lenroot e Giedd, 2010).

During adolescence, some regions of the brain are more sensitive to exposure to low doses of alcohol, such as the PFC, which can lead to future negative behavioural and cognitive consequences.

4. ALCOHOL POST-CONSUMPTION GENETIC PREDISPOSITIONS AND THEIR IMPLICATIONS IN ALCOHOL ADDICTION

In addition to social and psychological factors, genetic factors play a significant role in individuals' susceptibility to alcohol and their subsequent risk of developing addiction to this substance in the future, as well as their levels of consumption.

Two genes stand out in this context, which are involved in alcohol metabolism: aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 1B (ADH1B) (Edenberg, 2007). After being absorbed in the stomach, alcohol makes its way to the liver for metabolism. Firstly, alcohol dehydrogenase (ADH) transforms alcohol into acetaldehyde (a toxic compound responsible for nausea and rapid heart rate). Subsequently, aldehyde dehydrogenase (ALDH) converts acetaldehyde into acetate.

Several studies have demonstrated that alterations in these genes and different alleles lead to varied responses to alcohol exposure. One very common gene in East Asia, ALDH2*504K, leads to the inactivation of the ALDH enzyme, contributing to increased levels of acetaldehyde. Consequently, individuals with a copy of this gene will have an exacerbated response to alcohol, experiencing intense vomiting and tachycardia, thus avoiding excessive consumption (protective effect of this allele against alcohol abuse) (Li, Zhao e Gelernter, 2012).

Similarly in East Asia, a specific allele of ADH1B, ADHB1*47His, is very common (Li *et al.*, 2007). There are two variants of the ADH1B enzyme that have a higher rate of ethanol metabolism compared to the reference variant and its respective β1-ADH enzyme: ADHB1*47His (with a histidine at position 47) and ADH1B*370Cys (with a cysteine at position 370) (*Alcohol Research: Current Reviews*, [s.d.]). Like ALDH2*504K, it has been demonstrated that ADH1B*47His also has a protective effect against alcoholism, as increased metabolism leads to higher levels of acetaldehyde and the aforementioned symptoms of nausea, vomiting, dizziness, and confusion (Mulligan *et al.*, 2003).

Contrary to what was previously mentioned, the influence of certain genes on the initiation of alcohol consumption and subsequent dependence has also been demonstrated through analyses of single nucleotide polymorphisms (SNPs) in linkage studies and genome-wide association studies (GWAS). Linkage studies focus on analysing specific regions of interest, and the population and sample size in these studies often involve families with a higher prevalence of the traits of interest (Pulst, 1999). In this case, a linkage study conducted in several families with a history of alcohol dependence linked a region on chromosome 4p (responsible for the origin of certain subunits of the $GABA_AR$) to abusive alcohol consumption. Following SNP genotyping, a group of SNPs in the $GABA_{A2}R$ gene was identified, which demonstrated a strong influence and relationship with the occurrence of brain oscillations and a higher risk and prevalence of alcoholism (Edenberg *et al.*, 2004). Due to the need for a large number of family members for the detection of different genetic variants, GWAS gained strength by analysing the SNPs of the involved genes in a much larger population, allowing the detection of variables that cause more subtle effects (Uffelmann *et al.*, 2021). The first published GWAS revealed that two closely linked SNPs, located on chromosome 2q35, and another on chromosome 9 SNPs located in various genes, such as ADH1C, are strongly associated with alcohol addiction and dependence (Treutlein *et al.*, 2009).

With the advancement of science and technology, it has been established that even small genetic variants lead to different traits in personality and its various dimensions. Within

the realm of personality dimensions, we have endophenotypes that are hereditary and allow us to establish relationships, specifically in this case, with alcohol consumption (Chassin, Flora e King, 2004). Various cohort studies have demonstrated that individuals who are more extraverted, exhibit negative emotionality (tendency to experience negative emotions like sadness and anxiety), and have lower conscientiousness are more likely to develop alcohol dependence (engage in heavy alcohol consumption) and face a higher risk (Hakulinen *et al.*, 2015). Additionally, sensation seeking also shows a strong association with excessive alcohol consumption (Derringer *et al.*, 2010). Given that both sensation seeking and negative emotionality are proven to be moderately hereditary personality traits, this reinforces the impact of genetics in post-consumption alcohol outcomes (Koopmans *et al.*, 1995; Scott *et al.*, 2016).

5. IMPACT OF HEAVY ALCOHOL USE AND BINGE DRINKING ON THE ADOLESCENT BRAIN

Excessive alcohol consumption has detrimental effects on individuals, encompassing physical changes in the brain as well as cognitive and social impacts. Such behaviour alters one's behaviour, impulses, and overall functionality. Adolescents, whose brains are particularly sensitive to even low concentrations of alcohol, are expected to experience a more pronounced impact when engaging in the excessive consumption of this addictive substance (Spear e Varlinskaya, 2005).

Adolescence is a crucial stage for brain development, characterized by substantial structural and functional transformations. Both heavy alcohol consumption and binge drinking have been shown to have detrimental effects on the adolescent brain. Studies have provided evidence that these two patterns can cause structural changes in the brain, particularly a rapid decrease in cortex volume accompanied by delays in the development and maturation of white matter, leading to disruptions in its integrity (Luciana *et al.*, 2013). Moreover, specific brain regions involved in cognitive and emotional processing are affected by alcohol, resulting in consequences for decision-making, impulse control, and memory (Mota *et al.*, 2013).

A longitudinal study was conducted with the participation of 55 individuals aged between 9 and 23 years (after applying exclusion criteria, which included "dependence on other substances of abuse") to assess the structural effects of alcohol use initiation in adolescents. It was observed that there was a greater-than-expected decrease in grey matter and cortical thickness in the middle frontal gyral region, which is associated with inhibitory control and working memory. Additionally, evidence was found supporting the notion that

alcohol acts as a neurotoxin in the brain, causing a delay in the expected development of white matter in segments involved in motor function, recognition memory, and other functions (Luciana *et al.*, 2013). Through the use of diffusion tensor imaging (DTI), a non-invasive technique that evaluates the diffusion rate of water molecules throughout the brain's structural network, it was demonstrated that adolescent alcohol users, after an 18-month follow-up, exhibited disruptions in white matter integrity in various brain regions (e.g., longitudinal fasciculus). These individuals displayed weakened white matter integrity across different fibber tracts, resulting in decreased connectivity between these pathways (Bava *et al.*, 2013).

In a study conducted on a specific area of the hippocampus in adult rats previously exposed to intermittent ethanol during adolescence (AIE), it was proven that excessive alcohol consumption at a young age leads to long-term potentiation. As a result, the AIE-rats displayed heightened responses to stimuli of lower intensity compared to the control group. Using immunohistochemical and electrophysiological methods, it was demonstrated that there was an increase in the number of immature dendritic spines, accompanied by a state of enhanced synaptic plasticity (Risher *et al.*, 2015). Since the hippocampus is closely related to memory function, this study served as one of the explanations for the observed behaviours in adulthood among adolescents exposed to alcohol.

Normally, alcohol consumption is linked to the use of other addictive substances like tobacco and drugs, making it challenging to assess the individual impact and specific changes caused by alcohol alone. The advantage of studies conducted in rodents is the ability to analyse these effects more precisely, in contrast to longitudinal studies performed on adolescents, which do not provide the same level of individual evaluation. A cohort study with a 2-year follow-up demonstrated a strong association between adolescent binge drinking and difficulties in verbal memory and episodic memory performance (which were diminished). Adolescents who discontinued binge drinking during the follow-up period showed results similar to the control group (non-binge drinkers) (Mota *et al.*, 2013). Another longitudinal study, with an 8-year follow-up of adolescents aged 13 to 17, revealed that alcohol use had a negative impact on visuospatial functioning, leading to impairments in memory and attention functions (Tapert *et al.*, 2002).

As mentioned in this analysis, alcohol misuse during adolescence can disrupt the balance of neurotransmitters such as DA and serotonin, which can contribute to the development of mental health disorders like depression, anxiety, and addiction. The use of alcohol during adolescence has been found to disturb the functioning of the cholinergic system in a brain region called the basal forebrain, which is involved in important cognitive processes

like learning and memory. Several studies have demonstrated that repeated alcohol use in adolescence leads to a decrease in the number of neurons that show immunoreactivity to choline O-acetyltransferase (ChAT) in the basal forebrain (Fernandez e Savage, 2017). ChAT is the step limiting enzyme involved in acetylcholine (ACh) synthesis and a biomarker of cholinergic neurons. ACh is involved in various cognitive functions and is the neurotransmitter of the nervous motor system. ChAT transfers the acetyl group from Acetyl-CoA to choline, forming ACh, which is stored in vesicles until it is released upon an external or neuronal stimulus (Witzemann, 2007). This reduction in ChAT immunoreactivity has been associated with increased disinhibitory behaviour, higher engagement in risky behaviours, and impaired performance on tasks requiring cognitive flexibility in adulthood, even after alcohol use has ceased. These findings suggest that alcohol consumption during adolescence can have long-lasting effects on cognitive functions and behaviour, extending beyond the period of alcohol use (Ehlers *et al.*, 2011).

The assessment of the toxic effects of alcohol is commonly performed through assays conducted in rodents for several reasons. Due to ethical concerns, direct clinical trials involving humans are limited since the substance being studied can potentially cause harm to human health, thereby presenting numerous ethical dilemmas. Although rodents and humans have differences at the brain level, they also share some structural similarities and cellular processes (Beauchamp *et al.*, 2022), providing significant advantages for gaining new knowledge in this field. Moreover, in experimental assays with rodents, there is improved control over variables such as environmental factors, age, sex, alcohol dosage, and duration of exposure, resulting in more reproducible and reliable outcomes.

The disruption of neurogenesis and neuroinflammation are common processes observed in both adolescent rodents and humans following excessive alcohol exposure. A study conducted in male Sprague-Dawley rats, using immunohistochemical methods, demonstrated that ethanol exposure during adolescence resulted in reduced levels of doublecortin (DCX), an important biomarker for immature neurons. This reduction indicates cell death and disrupted neurogenesis. Neurogenesis is the process of generating new neurons in the brain, primarily occurring in specific brain regions such as the hippocampus. The decrease in DCX levels in the dentate gyrus (DG) of the hippocampus revealed that alcohol misuse impairs neuronal differentiation, potentially due to cellular death (Broadwater *et al.*, 2014). These effects contribute to long-term consequences on cognitive function and emotional regulation, which persist even after chronic alcohol consumption has ceased. Additionally, there is evidence of a persistent decrease in the subventricular zone (SVZ) of the

hippocampus, albeit for different reasons than in the DG (Liu e Crews, 2017). The SVZ contains neural stem cells and progenitor cells, collectively known as SVZ neuroprogenitors, which possess an incredible capacity for self-renewal and differentiation into various types of cells within the central nervous system (Sequerra, 2014). Disturbances in the SVZ neuroprogenitor population and differentiation processes are the main factors contributing to disrupted neurogenesis in the SVZ of the hippocampus. This alteration in neurogenesis, following alcohol exposure during adolescence, has been linked to behavioural changes in adulthood, such as a decrease in cognitive flexibility (Liu e Crews, 2017).

Neuroinflammation refers to the activation of the brain's immune response in reaction to injury or disease. Additionally, it is now well-known that neuroinflammation can also be triggered by drugs and other potential toxins. This immune response involves the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor α (TNF-α), as well as the activation of immune cells in the brain. In the case of adolescent alcohol exposure, this can lead to neuroinflammation. The brain's inflammatory response can be dangerous and harmful to the organ itself, as it can disrupt its normal functions. A study conducted on adolescent rats exposed to the AIE model demonstrated a significant increase in the levels of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Pascual *et al.*, 2007). COX-2 is an enzyme involved in the inflammatory cascade, responsible for the production of prostaglandins, and plays a crucial role in mediating pain and inflammation. On the other hand, iNOS is an enzyme that plays a fundamental role in the production of nitric oxide (NO), which is important for the body's defence mechanisms. This enzyme is induced by inflammatory stimuli, leading to a high production of NO that aids in cellular signalling processes. The study demonstrated that ethanol leads to excessive and prolonged levels of COX-2 and iNOS, which potentiate inflammation and, consequently lead to cell death in the hippocampus, cerebellum, and neocortex, as well as impairment in brain maturation. Furthermore, it was found that administering indomethacin, a non-steroidal anti-inflammatory drug (NSAID), helped alleviate and mitigate the deficits cause by AIE exposure (Pascual *et al.*, 2007).

Despite the mechanisms of alcohol still being uncertain, another pathway responsible for brain damage and alcohol-induced neuroinflammation is the activation of the immune receptor Toll-like receptor 4 (TLR4). A study conducted in mice demonstrated that TLR4-deficient mice did not experience the effects caused by ethanol compared to mice that had this receptor (Montesinos *et al.*, 2016). Normal mice underwent molecular changes accompanied by long-term behavioural effects associated with increased alcohol preference

and altered reward-related and anxiety-related behaviours. Binge drinking during adolescence also led to alterations in synaptic plasticity (changes in the connections between neurons) and epigenetic changes in the promoter region of two specific genes: the brain-derived neurotrophic factor gene (bdnf) and the fosB gene. The expression of these genes was found to be increased in the medial prefrontal cortex (mPFC), possibly contributing to the long-term behavioural effects observed in rats. Furthermore, these molecular changes that occurred in the mPFC can potentially contribute to the development of alcohol abuse and related disorders in adulthood (Montesinos *et al.*, 2016).

6. Interventions and Management Strategies for Alcohol Dependency

The management of alcohol dependence involves various approaches and requires much more than just cessation of consumption, although that is an excellent first step. It encompasses different types of interventions with varying durations, which can be carried out in ambulatory/outpatient settings, internment/inpatient facilities, or day centres. It necessitates the simultaneous involvement of pharmacological treatment, psychological intervention, social rehabilitation, among others. Treatment is a lengthy process that involves multiple stages and requires continuous motivation and determination, always striving to combat potential relapses (which, if they occur, indicate that adjustments are needed in the implemented treatment). Treatment is personalized and tailored to the individual, based on their specific characteristics and needs, hence the importance of being supported by healthcare professionals (*SICAD*, [s.d.]).

As mentioned earlier, treatment can be carried out either on an outpatient basis or through inpatient care, depending on the presented situation. Outpatient treatment is suitable for mild to moderate cases (first option), while inpatient care is considered the best option for more severe cases and higher levels of alcohol dependence. For instance, when severe withdrawal symptoms such as hallucinations or delirium tremens start to emerge, inpatient care becomes necessary.

The treatment of acute alcohol intoxication is primarily symptomatic, focusing on restoring fluid and electrolyte balance, addressing any associated comorbidities, and conducting a psychiatric evaluation. It is crucial to prevent alcohol dependence and to avoid the progression of this condition into chronic alcohol consumption (*Socidrogalcohol | Guía clínica alcohol, segunda edición*, [s.d.]). One of the main focuses in its treatment is the monitoring of

vital signs, assessing signs of possible trauma. The treatment depends on the severity of acute alcohol intoxication (AAI): mild/moderate AAI if blood alcohol concentration (BAC) is below 1g/L, and severe AAI if BAC is above 1g/L. In moderate AAI, continuous hydration is necessary (especially in cases of dehydration; 1500mL of 5% glucose solutions and saline), the patient is kept under observation for possible withdrawal symptoms, and there is no need for medication administration. In cases of severe AAI, restoration of fluid and electrolyte balance remains one of the main treatments, along with performing gastric lavage and providing mechanical ventilation support (Caputo *et al.*, 2019). Activated charcoal can only be administered within 2 hours after excessive consumption. If simultaneous consumption of alcohol and other substances is suspected, it justifies the administration of certain medications. Flumazenil (Sharbaf Shoar, Bistas e Saadabadi, 2023) is administered every 30 minutes to reverse the effects of benzodiazepines (BZDs) , as it acts as a competitive BZD antagonist, binding to the same site on the $GABA_A$ receptor as the BZDs (but with the opposite effect). In the case of opioid use, naloxone (Jordan e Morrisonponce, 2023), a competitive antagonist of mu opioid receptors, can reverse their effects and should be administered every 30 minutes due to its short half-life. Metadoxine is one of the substances that have shown evidence in reducing BAC and acetaldehyde levels. It is a compound derived from pyridoxine (vitamin B6) and pyrrolidone carboxylate, and according to certain studies, it is responsible for accelerating alcohol elimination and, consequently, speeding up the recovery from AAI (Shpilenya *et al.*, 2002). However, there are no studies on its use in children and adolescents. In children and adolescents, the treatment of AAI follows the same guidelines as in adults (Caputo *et al.*, 2019), but with additional concerns. In younger individuals, there is a higher risk of hypoglycaemia and hypothermia due to the effects experienced with the depression of the CNS. When BAC is elevated, it is extremely important to monitor symptoms associated with CNS depression, and the treatment focuses on correcting possible hypoglycaemia and hypomagnesemia. Instead of gastric lavage, antiemetics are administered to control nausea and vomiting. In cases of restlessness, the administration of haloperidol (Rahman e Marwaha, 2023), an antipsychotic that blocks dopamine D2 receptors, may be indicated to help manage symptoms (Caputo *et al.*, 2019).

The initial treatment of alcohol dependence focuses on facilitating GABAergic neurotransmission through indirect agonism of GABA and inhibiting glutamate and its excitatory action. In the early stage, we have the so-called "detoxification" phase, where the main objective is complete alcohol abstinence, and medications are used to treat symptoms associated with alcohol withdrawal, such as *delirium tremens*. During the acute withdrawal

phase, GABA neurotransmission is diminished, while glutamate concentrations increase, contributing to neuronal hyperexcitability. Therefore, the administration of BZDs is justified, as they facilitate GABAergic neurotransmission through their mechanism of action. BZDs are positive allosteric modulators of type A GABA receptors (ionotropic) (Elholm *et al.*, 2011). BZDs do not bind to the same receptor binding site as GABA itself, but rather to a different site, which increases GABA's affinity for its receptor. Some of the BZDs used include diazepam, lorazepam, and oxazepam (preferable in cases of hepatic insufficiency and elderly patients). Long-acting BZDs, such as diazepam, are preferred over short-acting ones, such as oxazepam, because the latter can potentially increase the risk of seizures during alcohol withdrawal (*Pharmacologic and Non-Pharmacologic Treatments for Alcohol Withdrawal in the Outpatient Setting: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines*, [s.d.]). Treatment begins with higher doses depending on the severity of the clinical condition, followed by a gradual tapering until discontinuation. These medications carry the risk of dependency and overdose, especially with the occurrence of relapses, which is why they are not recommended for maintaining abstinence. The administration of vitamin B1 is crucial as a preventive measure against the development of Wernicke-Korsakoff syndrome, a condition characterized by thiamine deficiency as mentioned earlier. Other vitamins such as vitamin B12, vitamin B6, and folic acid may also be administered. This acute withdrawal treatment phase typically lasts for 1 to 2 weeks (Palma, [s.d.]; Pereiro Gómez, 2010; *Socidrogalcohol | Guía clínica alcohol, segunda edición*, [s.d.]).

The second stage, a crucial phase in preventing relapses and maintaining motivation, is called the "relapse prevention phase" or "maintenance phase". In this phase, a combination of psychosocial therapies and specific pharmacological treatment is employed to control impulses and cravings. There are four substances approved by the European Medicines Agency (EMA) for the treatment of Alcohol Use Disorder (AUD): disulfiram, acamprosate, naltrexone, and nalmefene (Burnette *et al.*, 2022; Palma, [s.d.]; Pereiro Gómez, 2010; *Socidrogalcohol | Guía clínica alcohol, segunda edición*, [s.d.]). Often, the use of these medications (under the supervision of healthcare professionals) is accompanied by urine alcohol tests to monitor and detect potential relapses. Additionally, there are other substances that, although not approved for this specific therapeutic indication, have shown positive evidence in the treatment of AUD, and ongoing debates surround their use. These include topiramate, gabapentin, pregabalin and varenicline. Furthermore, new molecules are being developed and studied for the same indication (Burnette *et al.*, 2022; Liang e Olsen, 2014; Litten *et al.*, 2016).

Starting with approved molecules for this indication, disulfiram is an inhibitor of the ALDH enzyme, leading to the accumulation of acetaldehyde. As mentioned before, this accumulation results in unpleasant effects such as nausea, vomiting, confusion, and weakness, which discourage alcohol consumption. The severe effects caused by disulfiram necessitate careful evaluation during its introduction and regular assessments throughout the treatment (Stokes e Abdijadid, 2023). Certain studies have shown success in maintaining abstinence through the use of disulfiram, primarily due to its aversive response (which can also lead to adherence problems). Disulfiram is indicated specifically for maintaining abstinence and not for reducing alcohol consumption, as the interaction Disulfiram-ethanol can sometimes result in an emergency situation (Kranzler e Soyka, 2018). In recent years, disulfiram has emerged as a promising treatment for cocaine dependence, primarily because its main metabolite inhibits the enzyme dopamine beta-hydroxylase (DBH), which is responsible for converting dopamine into noradrenaline (Kosten *et al.*, 2013).

Acamprosate, also approved for the treatment of AUD, is involved in the modulation of the NMDA receptor. Initial studies have shown that it acts as a partial co-agonist, meaning that at low glutamate concentrations it potentiates the receptor, and at high glutamate concentrations it inhibits the receptor by competing with the neurotransmitter (Mason e Heyser, 2010). It has been demonstrated that acamprosate also acts as an antagonist of the mGluR5, and its effects are similar to those of an mGluR5 antagonist, called methylphenylethynylpyridine (Blednov e Adron Harris, 2008). It is believed that acamprosate also indirectly affects $GABA_A$ transmission (Kalk e Lingford-Hughes, 2014). By acting on the glutamatergic system, acamprosate helps reduce the risk of drinking and prolongs abstinence, as it is the glutamatergic hyperexcitability during chronic alcohol consumption that drives craving. An important characteristic of this substance is that there is evidence suggesting its neuroprotective effect. The up-regulation of NMDA receptors during withdrawal can lead to neurotoxicity and cell death, making acamprosate administration more advantageous due to its neuroprotective effects (Mason e Heyser, 2010). Therefore, acamprosate is recommended and approved for maintaining abstinence and for preventing relapses in individuals who are already abstinent before starting treatment (Burnette *et al.*, 2022).

Both naltrexone and nalmefene reduce the desire to drink by modulating the opioid system and blocking the reinforcing effects of alcohol (Niciu e Arias, 2013). These two substances act as antagonists of mu and delta opioid receptors. By antagonizing mu opioid receptors, they contribute to a decrease in DA release in the NAcc, due to an increase of GABA action on dopaminergic neurons in the VTA (Schreiber, Odlaug e Grant, 2013).

Recently, nalmefene has shown the particularity of acting also as a kappa opioid receptor partial agonist, further reducing the concentration of dopamine released in the NAcc (Browne, Smith e Lucki, 2020). Naltrexone and nalmefene will reduce motivation for self-administration and diminish the rewarding effects of alcohol. For these reasons, they have been approved to assist in reducing consumption in people with AUD (Burnette *et al.*, 2022).

Baclofen, which stimulates $GABA_B$ receptors, was approved for the treatment of AUD in France in 2018. Due to its agonism of $GABA_B$ receptors, it has shown to be beneficial in maintaining and prolonging abstinence. However, its adverse effects such as sedation and vertigo, associated risks including an increased risk of depression, and the life-threatening withdrawal syndrome associated with its discontinuation, as well as the inter-individual variability in its effectiveness, have hindered its use, and its use is still a subject of debate (Burnette *et al.*, 2022). The same applies to sodium oxybate (SMO), also known as the sodium salt of gamma-hydroxybutyrate (GHB). It acts as a partial agonist of $GABA_B$ receptors and also affects GHB receptors (Busardò *et al.*, [s.d.]). It has been proven effective in reducing withdrawal symptoms and increasing abstinence. However, its use in the treatment of AUD is only approved in Austria and Italy due to the risk associated with its consumption. Since GHB is used as recreational drug, the use of this salt is accompanied by a craving sensation and can lead to abusive situations (Burnette *et al.*, 2022).

As previous mentioned, there are other substances that, despite having different therapeutic indications, have shown positive evidence regarding their use in the treatment of AUD (used off-label). Topiramate, commonly used as an anticonvulsant, inhibits kainate and AMPA receptors, increases GABA activity, and blocks L-type calcium channels. By reducing the transmission, it influences the dopaminergic circuit and leads to a reduction in craving, contributing to a decrease in heavy drinking days (Burnette *et al.*, 2022; Litten *et al.*, 2016). It has been suggested as an option for individuals who are initiating treatment and are not completely detoxified (Kenna *et al.*, 2009). Pregabalin (Guglielmo *et al.*, 2012) and gabapentin (Mason *et al.*, 2014), also antiepileptic drugs, act as blockers of presynaptic L-type calcium channels, leading to a reduction in calcium influx and consequently decreasing the exocytosis of synaptic vesicles. As a result, they inhibit the release of glutamate, which is elevated during chronic alcohol consumption and withdrawal, reducing craving and preventing potential relapses (Burnette *et al.*, 2022; Litten *et al.*, 2016). Varenicline, which is approved for smoking cessation, acts as a partial agonist at α4β2 nicotinic ACh receptors and as a full agonist at α7 receptors, leading to an appropriate stimulation of dopamine release (Burnette *et al.*, 2022; Litten *et al.*, 2016). It also functions as a competitive antagonist by blocking the alcohol-induced

increase in dopamine when it acts on ACh receptors (McKee *et al.*, 2009). This mechanism of varenicline justifies the inhibition of alcohol reinforcement and craving. Certain studies have demonstrated that the administration of varenicline is a potential promising treatment for heavy-drinking smokers with low-severity AUD (McKee *et al.*, 2009). Co-administration with naltrexone has shown to bring benefits compared to separate administration of each substance.

The duration of the treatment depends on the individual's progress and can vary from weeks to several months, as determined by the healthcare professionals involved in their care. Psychological support is essential to ensure that individuals feel supported and can uncover the underlying causes of this problem. This type of support provides a safe space for individuals to express their feelings and helps them develop strategies to combat potential triggers, thus preventing relapses. Additionally, it assists in providing individuals with extra motivation to maintain their commitment to the primary treatment goal of sustained abstinence. Support groups are also available, where people can share their experiences and listen to others, creating a sense of mutual support while receiving support themselves (Palma, [s.d.]; Pereiro Gómez, 2010; *Socidrogalcohol | Guía clínica alcohol, segunda edición*, [s.d.]).

7. CONCLUSIONS AND FUTURE PERSPECTIVES

This review provides compelling evidence that alcohol addiction is increasingly becoming a significant societal issue, affecting both young individuals and adults. Despite the relatively stable statistical trends in alcohol consumption, the problem persists, leading to long-term physical and mental health complications.

Throughout the chapters, we have highlighted the adverse outcomes associated with alcohol consumption during adolescence and their potential impact on the future. Cognitive developmental delays and engagement in risky behaviours are just a few examples of the consequences stemming from alcohol dependence in teenagers. Genetic factors and environmental influences, such as social pressure during this critical stage of life or a family history of alcoholism, play a substantial role in the development of this problem.

It is necessary to constantly update the therapeutic range for AUD, as it has been proven that this disorder is heterogeneous, varying according to the characteristics of each individual, such as age, gender, comorbidities, presence of other psychiatric disorders, among others. There are several molecules that are still under development and being studied for the treatment of AUD. Both preclinical and clinical evidence point to cannabidiol (CBD) as a

promising therapy for excessive alcohol consumption (Burnette *et al.*, 2022). CBD interacts with different systems, such as the endocannabinoid system (acting as a negative allosteric modulator of cannabinoid receptors type 1 and type 2), the opioidergic system, and the serotonergic system. Recent evidence demonstrates that CBD consumption leads to a reduction in alcohol consumption, along with a decrease in motivation and relapse risk (De Ternay *et al.*, 2019). In addition, CBD has a low potential for abuse. Considering its beneficial effects and low abuse potential, CBD is one of the substances under discussion for future use in the treatment of AUD. Molecules such as GET*73* (a GHB analogue) and ASP8062 (a non-competitive positive allosteric modulator of $GABA_B$ receptor) have been under investigation in preclinical and clinical studies for the treatment of excessive alcohol consumption (Burnette *et al.*, 2022). It is important to note that further research is needed to fully understand their safety and efficacy profiles in treating alcohol abuse.

Similar to the developments in 2011 (World Health Organization. Regional Office for Europe, 2019), the WHO introduced a comprehensive plan in 2020, spanning from 2022 to 2030, aiming to address and mitigate the challenges posed by alcohol consumption and its associated risks (Montesinos *et al.*, 2016; *SICAD*, [s.d.]). Among the proposed strategies, a key focus is on reducing marketing activities and promotions related to alcoholic beverages. Special attention is directed towards safeguarding children, adolescents, and individuals in the abstinent phase, who are particularly susceptible to the influence of marketing efforts. Implementing prevention campaigns in schools serves as an effective approach to educate and inform young individuals about the consequences and negative risks associated with alcohol consumption. Furthermore, stringent control measures for accessing alcohol play a pivotal role in combating alcohol use during adolescence.

Effective collaboration among different stakeholders in society, including healthcare professionals, vendors, and teachers, is crucial to achieve a significant decrease in global levels of substance abuse and its harmful effects.

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