count and increased levels of the cytokine IL-6 and C-reactive protein in serum.

A growing body of evidence suggests that factors other than aging can result in a predisposition to CH and may be responsible for the wide variability in clonal dynamics across CH-positive people. Among genetically predisposing factors, the most notable involve the *TERT* loci and *TET2* variants[6]. Toxic exposures such as chemotherapy or radiotherapy are highly specific for mutations in *PPM1D*, *TP53* and *CHEK2*, and smoking is specifically associated with mutations in *ASXL1*[7]. Inflammation has been shown to strongly affect *TET2* clonal dynamics via increased IL-6 production[8] and to strongly affect *DNMT3A* clones via an immune response mediated by the cytokine IFN-γ[9]. Immune attack, as occurs in aplastic anemia, is associated with mutations in *BCOR* and *BCORL1*, suggestive of a role of autoimmunity in clonal selection[10]. Metabolic factors also contribute to a predisposition to CH, as demonstrated by the association of hyperglycemia and insulin resistance with mutations in *TET2*[11], and atherosclerosis has been shown to promote HSPC division and accelerate clonal evolution[12].

Common to most of the factors mentioned above is some form of chronic inflammatory dysregulation, which can be age related and of infectious, autoimmune or metabolic origin. Chronic inflammation has been shown to exhaust the native HSPC pool as a result of excessive differentiation, depleting its self-renewal capacity. CH-mutant HSPCs, on the other hand, demonstrate defective differentiation and enhanced self-renewal under the influence of certain pro-inflammatory cytokines and chemokines. Thus, repeated or sustained exposure to inflammatory stimuli might leave them at a competitive advantage. The studies presented in this issue[2,3] describe the role of CH as both a driver of inflammation (primary CH) and its consequence (secondary CH). This could be conceptualized chronologically as follows: low-grade inflammation initially promotes clonal expansion of certain mutant HSPCs that, as the clone size increases, further promotes inflammation in a vicious circle that ultimately compromises organ function.

Of note, CH can also be virtuous in nature. Studies have demonstrated its potentially beneficial effects in the context of bone marrow transplantation, through its association with chronic graft-versus-host disease and decreased risk of relapse[13]. Patients with aplastic anemia frequently develop CH characterized by mutations in *BCOR* and *BCORL1*; these patients' favorable outcome suggests that these mutations confer some fitness advantage to the clone, allowing it to evade immune attack by autoreactive T cells[10]. These adaptation mechanisms of the marrow, beneficial to the organism's fitness at some early point in time, yet carrying detrimental consequences on its fitness later on, are reminiscent of the 'antagonistic pleiotropy' theory of aging. Despite vast improvements in the understanding of CH, important questions remain unanswered. Further work is needed for full elucidation of the role of CH as both product and perpetrator of inflammation, as well as the specific contexts in which these may be harmful or beneficial. ❐

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Competing interests
The authors declare no competing interests.

Check for updates

PSYCHIATRY

Putting the MD back into MDMA

A phase 3 study shows that MDMA may be a promising treatment for PTSD, which will require a shift in how this drug is perceived.

David J. Nutt and Harriet de Wit

MDMA—colloquially known in its unregulated form as 'E' or 'ecstasy' in Europe and as 'molly' in the USA—is a small, amphetamine-like molecule that has had a rollercoaster reputational ride, from being positioned as a promising new therapeutic tool to being branded a brain-damaging recreational drug. Most of those historic fears were overstated, and recent empirical research, especially into the treatment of post-traumatic stress disorder (PTSD) and related conditions, is now bringing MDMA back into the medical fold. In this issue of *Nature Medicine*, Mitchell et al. report the first phase 3 study of MDMA, which reveals significant efficacy and an excellent safety profile in people with severe PTSD[1]. It now seems likely that it will be an approved medication in a few years.

MDMA was invented by Merck in 1912 as a precursor in a new synthesis for hemostatic substances[2]; Merck tested MDMA in animal models in 1927 and in 1959 but found nothing of interest. It was then resurrected by Alexander Shulgin in the 1970s, when he self-experimented with a range of phenylethylamine drugs. MDMA stood out as being different from other related compounds, as it provided greater clarity of thought and empathy with others. Shulgin introduced it to his wife, who was a psychotherapist, and she agreed it had therapeutic potential, particularly for couples counseling. The Shulgins made it available to other therapists in the USA, who found MDMA helpful in breaking down the hostile tensions and frictions that build up in many partnerships. For these

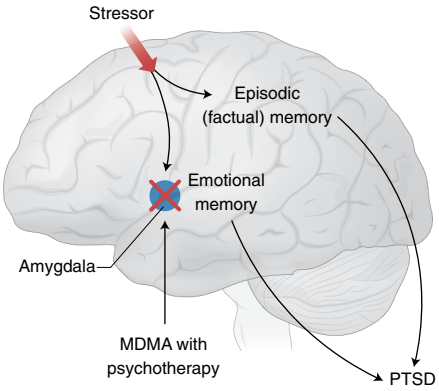

Fig. 1 | The brain pathways of PTSD and site of action of MDMA in therapy. A severe, life-threating stressor (trauma) leaves an emotional trace as well as a factual trace in different parts of the brain. Negative emotions are reactivated by remembering the trauma or as part of a conditioned fear reflex—for example, a car backfiring activates the memory and emotions of experiencing a gunshot. MDMA treatment facilitates the extinction of these emotional resurgences.

reasons, MDMA became known as the 'empathy' drug.

At that time in the 1970s, MDMA was legal, and this led to its downfall. Dealers realized that it was a legal alternative to amphetamines and cocaine, so they started to sell it and sought to enhance its market value by calling it 'ecstasy'. Its unique pro-social effects made it especially attractive at mass musical gatherings (raves), and it apparently lacked the problems of aggression and violence associated with other drugs such as alcohol or stimulants. The rave scene was less troublesome than traditional drunken gatherings from a policing point of view; however, the use of MDMA in public contexts attracted the attention of politicians while US President Reagan and his wife Nancy were ramping up the war on drugs.

The Reagans fueled a moral panic about this new drug with calls to ban it. The US therapists resisted, but, encouraged by misleading claims of brain damage, the US Drug Enforcement Administration criminalized MDMA in 1985. Recreational use continued, although clinical research effectively stopped. In 1986, a group of therapists established the Multidisciplinary Association for Psychedelic Studies (MAPS) to continue to explore the therapeutic utility of MDMA. By the end of the 1980s, MDMA was banned in most Western countries.

Despite the vast extra costs and bureaucratic constraints that the illegal status of MDMA introduced, clinical research by MAPS progressed. The first clinical study of MDMA, undertaken by the Mithoefer team, revealed its remarkable efficacy in the treatment of patients with chronic, therapy-resistant PTSD[3]. Since then, several phase 2 studies have shown similar therapeutic efficacy in similar patient populations, which led the US Food and Drug Administration to grant the Breakthrough Therapy designation to the MAPS program. The European Medicines Agency has also approved the protocol design for parallel phase 3 studies.

The phase 3 study reported in this issue[1] expands on substantial phase 2 research in the Americas and Europe; the study replicates the high efficacy seen in phase 2 trials for PTSD[3], with a similar tolerability profile. Furthermore, an open trial of MDMA treatment for alcohol-use disorder showed remarkably reduced drinking over 9 months[4]. If follow-up studies of these indications replicate positive efficacy with MDMA and the current good safety profile is sustained, then it seems likely that MDMA will be approved as a treatment for PTSD and alcohol-use disorders, to be used in specific psychotherapy settings with trained therapists.

What is remarkable about MDMA therapy is that large clinical effects are produced by just two or three doses, given a few weeks apart in a structured psychotherapy program. This represents a very novel type of pharmacological intervention, very different from any available in psychiatry today. So how does MDMA do this?

Pharmacologically, MDMA resembles amphetamines, but it has greater impact on serotonin. MDMA is also an agonist of the 5-HT2 family of serotonin receptors[5]. Enhanced serotonergic function may explain its 'empathogenic' effects, achieved either directly or indirectly by increasing levels of oxytocin, which is known to be involved in social function and which a recent rodent study suggests may open a critical window in cortical functioning, allowing learning of new behavioral responses[6].

At the psychotherapeutic level, MDMA facilitates exposure therapy. It is the sudden, reflex re-emergence of the emotions that were present during the initial trauma that makes PTSD so distressing. Therefore, current treatments aim to reactivate and then extinguish this emotional memory[7] (Fig. 1). In healthy volunteers, MDMA reduces the impact of negative memories, whether they are autobiographical or induced by negative stimuli encountered as part of a controlled study[8,9], consistent with its therapeutic value. Human neuroimaging has provided a plausible mechanism for this effect, whereby MDMA suppresses activity of the amygdala in response to negative stimuli[9,10]. MDMA also enhances social connections and thus facilitates the therapeutic process in this aspect[11,12].

Of course, more needs to be done to convince the medical community, regulatory agencies and the public of the efficacy and safety of MDMA. The many mistruths perpetuated about this drug as well as its current Schedule I classification (applied to drugs with a strong potential for abuse and no accepted medical use) serve only to fuel fears about its harm and addictive potential, which greatly limits its accessibility. The new evidence published by Mitchell et al.[1] supports the efficacy and safety of MDMA after just a few exposures at a relatively moderate dose, without signs of tolerance or dependence.

MDMA treatment gives hope and excitement to a field in which outcomes have been historically very poor. Rescheduling MDMA to a lower level of restriction in the UK and USA would greatly accelerate research and make it more accessible to those in need; the World Health Organization and United Nations should consider doing the same. ❐

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Competing interests

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