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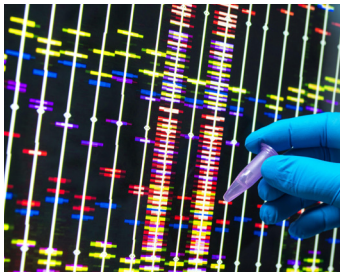

Clinical value of genome targeted cancer therapies p 185

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ORIGINAL RESEARCH Cross sectional study

Clinical value of guideline recommended molecular targets and genome targeted cancer therapies

Tibau A, Hwang TJ, Avorn J, Kesselheim AS

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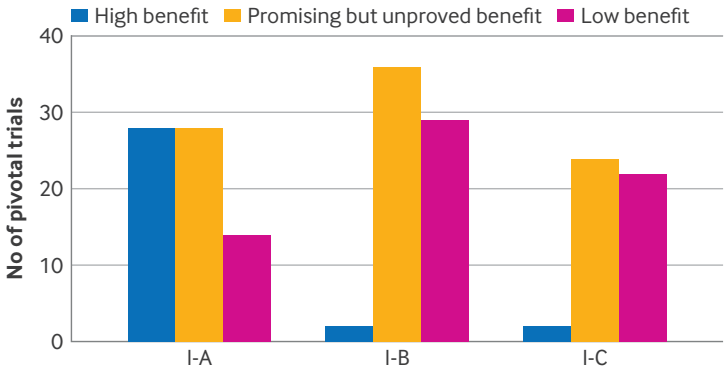
Study question What are the clinical benefits and actionability of molecular targets for NCCN (National Comprehensive Cancer Network) recommended genome targeted cancer drugs for clinical practice?

Methods Trial design characteristics and outcomes were obtained from publications supporting NCCN recommendations for genome targeted cancer drugs in the advanced setting. Molecular target actionability was assessed using the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT). The clinical benefit of therapies was evaluated using the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). Molecular targets at ESCAT category I with ESMO-MCBS grades 4 or 5 were classified as being of high benefit. Targets with an ESCAT category I and ESMO-MCBS grade of 3 were categorised as treatments with promising but unproved benefit.



Value of molecular targets recommended by NCCN guidelines. I-A, IB, and I-C are ESCAT tiers

Study answer and limitations Among 411 recommendations for 74 genome targeted drugs, 12% (32/267) of scorable trials showed substantial clinical benefit and 33% (88/267) endorsed genome based cancer treatments with promising but unproved benefit. Of the 118 interventions endorsed by NCCN authors as preferred, 62 (53%) applied to treatments with high or promising but unproved benefit. Most (76%; 262/346) of the cohort's trials were single arm, resulting in only a few meeting the ESMO-MCBS criteria for substantial clinical benefit.

What this study adds About one eighth of genome targeted cancer therapies in NCCN guidelines for metastatic cancer were of high benefit, and one third were of promising but unproved benefit, according to the ESCAT and ESMO-MCBS frameworks.

Funding, competing interests, and data sharing See full paper on bmj.com for details.

Doctors and suicide

ORIGINAL RESEARCH Gender stratified systematic review and meta-analysis

Suicide rates among physicians compared with the general population in studies from 20 countries

Zimmermann C, Strohmaier S, Herkner H, et al

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Study question What are the age standardised suicide rate ratios for male and female physicians compared with the general population?

Methods Studies published between 1960 and 31 March 2024 were retrieved from Embase, Medline, and PsycINFO. Observational studies providing age standardised mortality ratios for physician deaths by suicide, suicide rates per 100 000 person years, or extractable data suitable for calculating ratios were eligible for inclusion. Risk of bias was assessed with an adapted version of the Joanna Briggs Institute checklist for prevalence studies. Random effects models were used to calculate mean effect estimates for male and female physicians, with a secondary analysis of deaths by suicide in physicians compared with other professions.

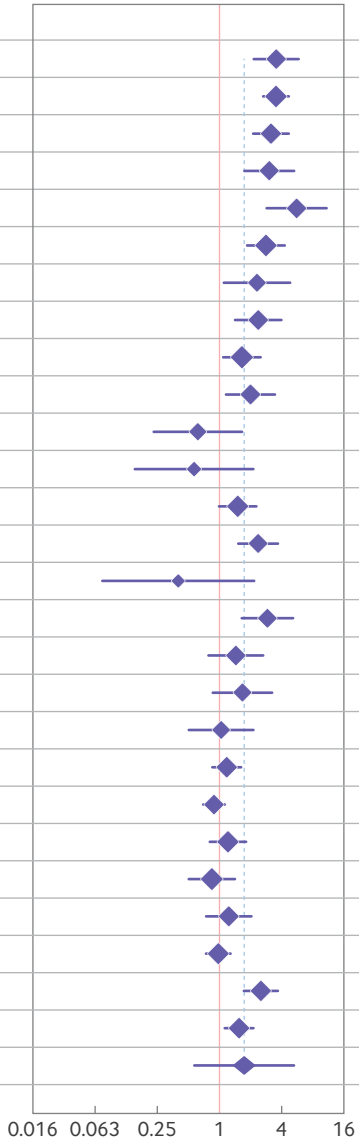
Study answer and limitations After full text screening, 38 studies for male physicians and 26 studies for female physicians were eligible for analyses, with a total of 3303 suicides in male physicians and 587 in female physicians. Across all studies, the suicide rate ratio for male physicians was 1.05 (95% confidence interval 0.90 to 1.22), while for female physicians the rate ratio was increased, at 1.76 (1.40 to 2.21). A high degree of heterogeneity was observed across studies, partly owing to a reduction in effect sizes over time. The suicide rate ratio for male physicians compared with other professions was 1.81 (1.55 to 2.12). Limitations include the small number of studies from regions outside the US, Europe, and Australia, which could affect the generalisability of the findings.

What this study adds While age standardised suicide rate ratios for male and female physicians have decreased over time, the risk of suicide in female physicians is higher than in the general population. A high level of heterogeneity across studies suggests that suicide risk varies among different physician populations.

Funding, competing interests, and data sharing Partially supported by the Vienna Anniversary Foundation for Higher Education. No competing interests declared. Data available from corresponding author on request.

Study registration PROSPERO CRD42019118956.

Study	Suicide rate ratio (95% CI)	Weight (%)	Suicide rate ratio (95% CI)
Craig and Pitts 1968		3.87	3.55 (2.14 to 5.89)
Pitts et al 1979		4.44	3.57 (2.67 to 4.77)
Bämayr and Feuerlein 1986		4.18	3.21 (2.16 to 4.77)
OPCS England and Wales 1986		3.70	3.10 (1.77 to 5.43)
Arnetz et al 1987		3.37	5.70 (2.91 to 11.16)
Stefansson and Wicks 1991		4.14	2.85 (1.89 to 4.30)
Herner 1993		3.11	2.32 (1.09 to 4.96)
Lindeman et al 1997		3.82	2.40 (1.42 to 4.04)
Juel et al 1999		4.16	1.68 (1.12 to 2.52)
Hawton et al 2001		3.76	2.02 (1.18 to 3.46)
Innos et al 2002		2.51	0.62 (0.23 to 1.66)
Shin et al 2005		1.81	0.57 (0.15 to 2.15)
Meltzer et al 2008		4.14	1.52 (1.01 to 2.30)
Petersen and Burnett 2008		4.06	2.39 (1.54 to 3.71)
Skegg et al 2010		1.30	0.40 (0.07 to 2.18)
Aasland et al 2011		3.64	2.93 (1.63 to 5.25)
Palhares-Alves et al 2015		3.56	1.45 (0.79 to 2.67)
Claessens 2016		3.37	1.68 (0.86 to 3.29)
Davis et al A 2021		3.25	1.04 (0.51 to 2.13)
Davis et al B 2021		4.36	1.17 (0.85 to 1.63)
Gold et al 2021		4.45	0.89 (0.67 to 1.18)
Ye et al 2021		4.18	1.22 (0.82 to 1.82)
Herrero-Huertas et al 2022		3.82	0.84 (0.50 to 1.42)
FSO Switzerland 2008-2020		3.87	1.23 (0.74 to 2.04)
ONS England 2011-2020		4.49	0.97 (0.74 to 1.28)
Petrie et al 2023		4.25	2.55 (1.76 to 3.68)
Zimmermann et al 2023		4.40	1.55 (1.14 to 2.11)
Overall		100.00	1.76 (1.40 to 2.21)



Forest plot of suicide rate ratios for female physicians compared with general population. See full paper on bmj.com for details of references

According to some estimates, one doctor dies by suicide every day in the US,[1] and around one every 10 days in the UK.[2] This high rate is borne out by Zimmermann and colleagues' meta-analysis,[3] which includes 64 observational studies on male (38 studies) and female (26 studies) doctors who died by suicide. These studies, with observation periods from 1935 to 2020 and from 1960 to 2020, respectively, report a suicide rate ratio of 1.05 (95% confidence interval (CI) 0.90 to 1.22) for male doctors, indicating no overall increase in risk compared with the general population. For female doctors, however, the suicide rate ratio was significantly increased, at 1.76 (1.40 to 2.21). The authors also found that while standardised suicide rate ratios for all doctors had decreased over time, the risk remained higher for female doctors compared with the general population.

A strength of this study is that it includes searches extending to March 2024, providing the most comprehensive picture to date of suicide risk among male and female doctors. The authors acknowledge potential study limitations, including scarcity of studies from outside Europe, the US, and Australasia; high heterogeneity in findings among included studies; and likely underreporting of suicide as the cause of death because of stigma. However, their findings are broadly similar to those of previous studies, including meta-analyses.[4-6]

The reasons behind any doctor's death by suicide can be perplexing; even bereaved relatives often struggle to understand their loved one's motivation.[7] The American psychiatrist Michael Myers, in his book *Why Physicians Die by Suicide*, writes that the act of suicide is a complex phenomenon involving the "convergence of genes, psychology, and psychosocial stressors that come together in a perfect, albeit horrific storm."[8]

Complex phenomenon

Doctors share risk factors with their non-medical peers, including family history of suicide, past experiences of trauma or abuse, isolation, mental illness, or drug misuse. However, they have additional

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Persistently high rates of suicide among female doctors need particularly urgent attention

risks, including a high risk of burnout[9] and barriers to accessing timely help for poor mental health.[10] Selection for the medical profession favours personality traits such as perfectionism, obsessiveness, and competitiveness,[11] which in highly stressful work environments can result in a triad of guilt, low self-esteem, and a persistent sense of failure.[12] Doctors also have access to potentially dangerous drugs, including opiates and anaesthetic agents such as propofol, which have been implicated in the relatively high rate of suicide documented among anaesthetists.[13]

While causal inference is not possible from observational studies, some have reported links between mental illness and suicide and being the subject of a complaint or regulatory processes.[14] The protracted nature of complaints processes could also play a part. In one UK study, doctors receiving a complaint of any kind were significantly more likely to report moderate to severe depression than those who had never experienced a complaint (relative risk 1.77, 95% CI 1.48 to 2.13).[15] Doctors with current or recent complaints were two times more likely than others to report thoughts of self-harm or suicidal ideation. Distress and suicidal ideation increased with the severity of the complaint, and levels were highest after a referral to the regulator. A study in the Netherlands reported similar findings.[16]

Addressing systemic issues

As Zimmermann and colleagues make clear, their analyses highlight an ongoing need to reduce mental distress and suicide risk among doctors, particularly women. This means addressing longstanding systemic issues that create distress, such as poor work and regulatory cultures that name, blame, and shame people when mistakes or complaints occur rather than looking to correct the broader system. It means adopting working schedules that allow doctors a sensible work-life balance, and paying attention to the basic emotional and psychological needs of all staff. Doctors should have timely access to psychological support, particularly during periods of high stress, such as during complaints or serious incident investigations.[17 18]

Persistently high rates of suicide among female doctors need particularly urgent attention from researchers, health leaders, and policy makers, including studies to explore likely contributors such as discrimination and sexual harassment, to characterise those at highest risk, and to develop gender specific interventions to protect female doctors' mental health. Finally, all doctors must have access to early intervention and confidential treatment services so they do not suffer in silence.[19]

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Find the full version with references at http://dx.doi.org/10.1136/bmj.q1758

If you're struggling, you're not alone. In the UK and Ireland, Samaritans can be contacted on tel 116 123 or jo@samaritans.org

Comparative oral monotherapy of psilocybin, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, ayahuasca, and escitalopram for depressive symptoms

Hsu T-W, Tsai C-K, Kao Y-C, et al

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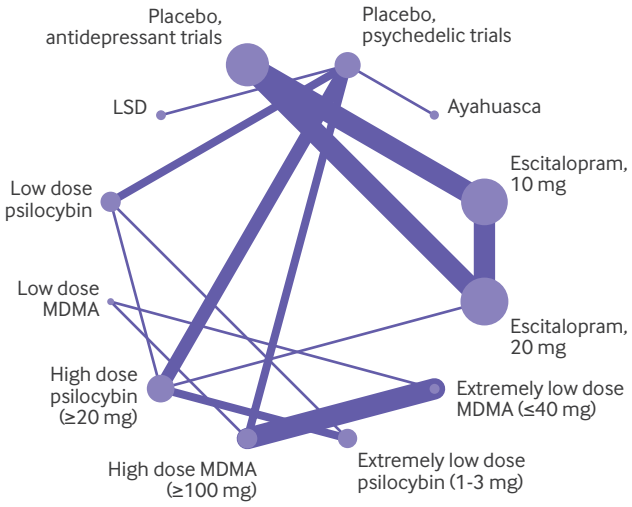
Study question What is the comparative effectiveness of using psychedelics versus escitalopram in patients with depressive symptoms, accounting for the potential overestimation of psychedelic effects due to unsuccessful blinding?

Methods Six databases were systematically searched for randomised controlled trials of adults with depressive symptoms who received one of four psychedelics (3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), psilocybin, and ayahuasca) without concomitant use of antidepressants, or who received escitalopram. The primary outcome was mean difference in depressive symptoms, as measured by the 17 item Hamilton depression rating scale. Data were pooled using a random effects model within a bayesian framework. To avoid estimation bias, the placebo responses in psychedelic and antidepressant trials were separated.

Study answer and limitations The placebo response in the psychedelic trials was lower than that in the antidepressant trials (mean difference −3.79 (95% credible interval −6.80 to −0.77)). Among all psychedelics, only high dose psilocybin (≥20 mg) was associated with greater effectiveness than placebo response in antidepressant trials and escitalopram. Although all available studies were included, the sample size of the psychedelic randomised controlled trials was small (k=15).



Network structure. LSD=lysergic acid diethylamide; MDMA=3,4-methylenedioxymethamphetamine

What this study adds The antidepressant effect of psychedelics might be overestimated, but the effectiveness of high dose psilocybin is significantly greater than that of placebo and escitalopram.

Funding, competing interests, and data sharing The study was supported by a grant from the National Science and Technology Council (NSTC 112-2314-B-016 -036-MY2). No competing interests declared. Data are available from the corresponding author (CSL) on reasonable request.

Study registration PROSPERO CRD42023469014.