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Bleuler revisited: on persecutory delusions and their resistance to therapy

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body-mass index, global assessment of functioning); medication history (antidepressants, antipsychotics, benzodiazepines, lithium); psychiatric and medical comorbidity; functional domains (including activities of daily living), and health service use. However, in such datasets, fine grained information is not readily available, and therefore comparisons such as unilateral versus bilateral electroconvulsive therapy cannot be made, and more subtle clinical details, such as retrograde amnesia, cannot be assessed. Kaster and colleagues' finding in regard to suicide—which was assessed at only 30 days after electroconvulsive therapy—is surprising, and although only a secondary analysis, and with small absolute numbers, makes the case for considering the use of electroconvulsive therapy stronger.

What do we make of this study, and is it relevant to debates on the use of electroconvulsive therapy? The data from Kaster and colleagues' study advance knowledge on potential risks associated with electroconvulsive therapy, and although there are inevitable problems with the method, it is worth noting that in a reasonably powered sample there was little to suggest increased risk, and, although the numbers are small, the data suggested potentially beneficial effects on suicide. Although these findings require replication, this study does provide the field with a considerable degree of reassurance about the safety of one of the most effective treatments within psychiatry.

SJ has received honoraria for educational talks given for Sunovion, and his employer, King's College London, has received honoraria for educational talks he has given for Lundbeck. AHY reports paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: AstraZeneca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, and COMPASS; is a consultant to Johnson & Johnson and Livanova; received honoraria for attending advisory boards and presenting talks at meetings organised by LivaNova; and was principal investigator in the Restore-Life VNS registry study funded by LivaNova, principal investigator on ESKETINTRD3004: "An open-label, long-term, safety and efficacy study of intranasal esketamine in treatment-resistant depression", principal investigator on "The effects of psilocybin on cognitive function in healthy participants", and principal investigator on "The safety and efficacy of psilocybin in participants with treatment-resistant depression (P-TRD)". This work presents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

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- 1 Kirov G, Jauhar S, Sienaert P, Kellner CH, McLoughlin DM. Electroconvulsive therapy for depression: 80 years of progress. *Br J Psychiatry* 2021; published online March 18. <https://doi.org/10.1192/bjp.2021.37>.
- 2 Semkowska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry* 2010; **68**: 568–77.
- 3 Tørring N, Sanghani SN, Petrides G, Kellner CH, Østergaard SD. The mortality rate of electroconvulsive therapy: a systematic review and pooled analysis. *Acta Psychiatr Scand* 2017; **135**: 388–97.
- 4 Jørgensen MB, Rozing MP, Kellner CH, Osler M. Electroconvulsive therapy, depression severity and mortality: data from the Danish National Patient Registry. *J Psychopharmacol* 2020; **34**: 273–79.
- 5 Kaster TS, Vigod SN, Gomes T, Sutradhar R, Wijeyesundera DN, Blumberger DM. Risk of serious medical events in patients with depression treated with electroconvulsive therapy: a propensity score-match, retrospective cohort study. *Lancet Psychiatry* 2021; **8**: 686–95.
- 6 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; **70**: 41–55.



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In schizophrenia spectrum disorders, antipsychotics are the mainstay of treatment. With a median effect size of 0.42,¹ they reduce overall symptoms such that many patients can live relatively stable lives in their own environment rather than being institutionalised, as was often the case before the 1950s. Persecutory delusions, however, a common and highly disabling feature of such disorders, remain notoriously difficult to treat. Paul Eugen Bleuler as early as 1908 that such delusions could linger on for decades, even when people were apparently cured.² A study published in 2010 of 200 patients diagnosed with schizophrenia showed that more than 50% of patients had frequent

delusional reasoning for another two decades, often despite adequate antipsychotic treatment.³ A traditional explanation for this finding is the chronicity of the underlying disease process, conceptualised in terms of neurobiology and psychosis-proneness. However, there are other explanations for the therapy resistance of persecutory delusions. First, delusions can be understood as extremes of distrust, and the basic capacity for distrust is adaptive; treating the capacity itself is neither feasible nor desirable. Second, affect-laden memories that are often inextricably intertwined with delusions are frequently powerful and long lasting. Lastly, persecutory delusions might

serve the function of providing a paradoxical sort of comfort to patients, especially when they feel lonely and isolated.

To complement the pharmacotherapy of persecutory delusions, cognitive behavioral therapy for psychosis (CBTp) is recommended as an evidence-based adjunct to medication in the treatment of psychosis.⁴ As shown in a meta-analysis published in 2020, CBTp is effective compared with treatment-as-usual or control conditions in reducing delusions (effect size 0.37), but not when compared with an active control such as befriending,⁵ operationalised as talking to a health professional as if they were a good friend.^{6,7}

Daniel Freeman and colleagues⁸ have been developing and testing a more personalised, translational treatment in which psychological risk and maintenance factors that drive threat beliefs are targeted one-by-one with brief CBT modules selected via client preference (including excessive worry, negative self-beliefs, disrupted sleep, reasoning bias, and others). In their randomised controlled trial of 130 patients diagnosed with non-affective psychosis, the Feeling Safe Programme led to a recovery rate for delusions of 50.8%, compared with 34.9% in the befriending group. The authors correctly describe these results as “the largest treatment effects for persistent delusions reported to date”, with effect sizes of 0.86 for delusional conviction and of 1.2 for delusion severity. Delusion severity halved in 21 (32.8%) patients in the Feeling Safe group versus 9 (13.6%) patients in the befriending group. The difference between the Feeling Safe Programme and befriending was moderate in terms of clinical significance, and the pattern of efficacy differences is consistent with the programmes’ aims: Feeling Safe affected positive symptoms, but also anger, psychological wellbeing, and other important outcomes, which in turn might help to reduce paranoia. This finding supports the validity of The Feeling Safe Programme. Key to the programme’s success appear to be the continuation of treatment-as-usual (ie, CBT delivered by highly qualified clinicians) and the addition of individually chosen modules, potentially increasing autonomy and empowerment, as well as decreasing dropout.

However, two core challenges deserve to be highlighted. First, the authors obtained effect size estimates by calculating the adjusted mean difference of the outcome between the Feeling Safe Programme

and befriending, divided by the pooled outcome SD at baseline. This is common practice and consistent with the study’s protocol, but because of a ceiling effect of the outcomes at baseline, the baseline outcome SD is around 2.5 times smaller than the 6 month outcome SD, which likely inflated effect sizes considerably. Second, both treatment conditions show remarkable pre-post effects compared with previous literature. This pattern of findings implies that major therapeutic effects of both interventions might occur through common factors, such as exposure and social contact. Elements of exposure have been shown to increase treatment effects in a range of anxiety-related disorders,⁹ and as observed already by Bleuler, meaningful social contact might still be the most powerful antidote against persecutory delusions: it is “paramount [...] that patients never lose contact with their surroundings [and] shut themselves out”.²

A further issue to consider is that the Feeling Safe Programme relies heavily on components of CBT, but it is not always clear to us where exactly the differences lie between CBTp and the Feeling Safe Programme. Moreover, although we strongly support the personalised approach to treatment, this poses interesting challenges to understand the working mechanisms of the Feeling Safe Programme. Finally, although the programme’s short-term results appear nothing but substantial, long-term follow-up of patients will be required to assess prognosis.

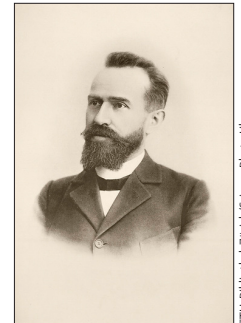
In sum, the Feeling Safe Programme is a well conducted study, but it remains to be seen whether the large effect sizes for either group will replicate in real-world settings with less specialised and trained therapists, and whether the large effect size for the Feeling Safe Programme versus befriending will replicate when no ceiling effects are present that impact effect size calculation.

We declare no competing interests. We thank Dr Helga Ising for helpful feedback on the draft.

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- 1 Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019; **394**: 939–51.
- 2 Bleuler E. Die Prognose der Dementia praecox (schizophreniegruppe). *Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin* 1908; **65**: 436–64.



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- 3 Harrow M, Jobe TH. How frequent is chronic multiyear delusional activity and recovery in schizophrenia: a 20-year multi-follow-up. *Schizophr Bull* 2010; **36**: 192–204.
- 4 National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. 2014. <https://www.nice.org.uk/guidance/cg178> (accessed June 2, 2021).
- 5 Turner DT, Burger S, Smit F, Valmaggia LR, van der Gaag M. What constitutes sufficient evidence for case formulation-driven CBT for psychosis? Cumulative meta-analysis of the effect on hallucinations and delusions. *Schizophr Bull* 2020; **46**: 1072–85.
- 6 Sensky T, Turkington D, Kingdon D, et al. A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Arch Gen Psychiatry* 2000; **57**: 165–72.
- 7 Jackson HJ, McGorry PD, Killackey E, et al. Acute-phase and 1-year follow-up results of a randomized controlled trial of CBT versus befriending for first-episode psychosis: the ACE project. *Psychol Med* 2008; **38**: 725–35.
- 8 Freeman D, Emsley R, Diamond R, et al. Comparison of a theoretically driven cognitive therapy (the Feeling Safe Programme) with befriending for the treatment of persistent persecutory delusions: a parallel, single-blind, randomised controlled trial. *Lancet Psychiatry* 2021; **8**: 696–707.
- 9 Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JAJ, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: a meta-analysis of randomized placebo-controlled trials. *Depress Anxiety* 2018; **35**: 502–14.



The unaddressed mental health burden among cancer patients in China: a call to action



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Despite advances in cancer prevention and control strategies in the past few decades, the cancer burden remains high in China, with years of life lost per 100 000 population ranging from 541 to 1065 for stomach, liver, and lung cancers in 2017.¹ According to the GLOBOCAN 2020 online database, cancer in China comprised approximately 24% of new cases and 30% of cancer deaths worldwide in 2020.

A largely unaddressed comorbidity associated with cancer in China is common mental health disorders, which constitute a major psychological burden. Chinese patients with cancer have high prevalence of depression (54.9%) and anxiety (49.7%),² and a higher suicide rate (63.17 per 100 000 person-years) than patients in Europe (39.28) and North America (32.27).³ Common mental health disorders impede patients' treatment, adherence, and adoption of a healthy lifestyle, which might contribute to the increasing cancer burden in China. Moreover, the unmet need for psychosocial support for caregivers also adds to the mental health burden in patients with cancer. In China, cancer caregiving responsibilities are primarily taken by family members, instead of hired professional caregivers, because of collectivist values and filial piety within Chinese culture, as well as an absence of an established professional caregiver training system. This elevated caregiving burden, coupled with the financial pressure resulting from reduced employment hours, can impair family caregivers' emotional well-being,⁴ which might compromise the quality of caregiving and the emotional support family can provide to patients.

Despite the noticeable mental health burden, Chinese patients with cancer face multiple barriers to accessing good-quality psychological services. First, resources for mental health care are scarce and are poorly integrated with cancer services. Despite the growth of the mental health-care system, trained mental health specialists continue to have little experience and expertise in treating patients with cancer. Although psychosocial interventions targeting patients with cancer in China have indicated promising effects in reducing psychological distress, most of these programmes were led by oncology nurses in tertiary cancer centres, who do not have substantial training in psychiatric care and are highly occupied by routine patient care demands.⁵ This could undermine the scalability and long-term maintenance of the therapeutic effectiveness of these interventions. In addition, disparities in access to mental health services are notable, with patients in economically poorer cities having even more restricted access to good-quality mental health care than patients in metropolitan cities, such as Beijing and Shanghai.

The double burden of cancer stigma and mental illness stigma, both of which are common in China,^{6,7} acts as a key barrier to provision of mental health services for patients with cancer. In Chinese culture, cancer is perceived as a contagious disease or death sentence for moral misconduct by patients or their ancestors.⁶ Similarly, individuals with psychological disorders are often regarded as dangerous or a shame to their families.⁷ Stigma might discourage patients from seeking support because of fear of disclosing their condition. Moreover, as Chinese culture encourages