Mental health needs of stay-in-hospital caregivers in China

The shortage of nursing staff in China has long been a serious problem, with a nurse to doctor ratio of about 1·2:1. This situation is exacerbated by violence against nurses, as reported by Peng Xiong and colleagues (June, 2016).[1] There might be no easy way to remedy this situation in a short time, but non-professional individuals, such as caregivers, might fill the gaps and could effectively deliver health care, especially mental health care.[2]

In mainland China, stay-in-hospital caregivers have already taken over about 10–20% of nursing work in general hospitals and mental health centres, especially in cities such as Shanghai, said Yi Xu, the nurse responsible for caregiver management in Zhongshan Hospital, Fudan University (personal communication). Most of these caregivers are women from rural areas. They cannot formally work in the ward until certificated by a local nursing association, which means taking a training course provided by the association and being supervised by a nurse for about 3 months. This training covers general nursing skills, such as aspiration of sputum and helping patients to turn over periodically, but little in terms of mental health care.

This means that the caregivers have little knowledge about mental health and mental disorders, such that, for example, when patients suffering from dementia present with behavioural symptoms, inexperienced caregivers do not know what the symptoms mean or what action to take, and are consequently frustrated. Conversely, the caregivers usually work and stay in a ward 24 h a day and almost 365 days a year, providing constant, long-term care. The caregivers have little support from their family when they encounter stressful events. Many of them have problems with sleep, but few seek help even though they work in a hospital. The numbers of reports on the mental health and wellbeing of migrant workers[3] and caregivers working in the community[4] in China are increasing, but few address this specific population and how best to support them.

There are various approaches to increase the knowledge on mental health and wellbeing of these caregivers. Findings from research in low-income and middle-income countries show a brief educational intervention reduced distress for family caregivers who take care of people with dementia.[2] Investigation into whether education would have a similar effect for stay-in-hospital caregivers would be worthwhile. Use of Balint groups, in which groups of clinicians meet and discuss cases to deal with their negative feelings such as anger and frustration, could be another approach. These meetings help physicians overcome occupational burnout and are now applied to reduce the distress of medical staff in general hospitals in China.[5] The coverage of Balint groups could be extended to the stay-in-hospital caregivers to enhance their wellbeing and thus the health of their patients.

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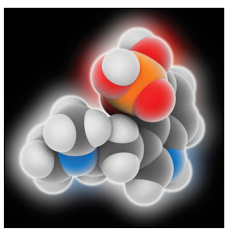
Psilocybin: panacea or placebo?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We write with reference to the study on psilocybin for treatment-resistant depression, reported by Robin L Carhart-Harris and colleagues in *The Lancet Psychiatry*.[1] Although we are relieved that attention is once again being given to basic research into depression—after the hiatus created the effective abandonment of this area of research by Big Pharma from 2010 onwards[2]—we are nonetheless deeply concerned that the mistakes that led to this withdrawal[3] are in danger of being repeated. Carhart-Harris and colleagues' study included 12 patients, and although the investigators reported that eight patients achieved complete remission at 1 week, only five of these patients were still in complete remission after 3 months of follow-up. The investigators concluded that this finding provides preliminary support for the safety and efficacy of psilocybin. The safety aspects are not at issue, but findings from a number of meta-analyses[4,5] now indicate that placebo alone can account for remission in approximately 40% of patients in this setting. Regrettably for the investigators' conclusions with respect to efficacy, this figure matches almost exactly the 42% (ie, 5/12) of patients they report as showing remission after 3 months. Further studies are of course always welcome, but we must be very careful not to be blinded in our critical thinking in this context by hopes that serendipity can provide answers that science has so far failed to provide.

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Question-based Drug Development for psilocybin

In *The Lancet Psychiatry*, Robin Carhart-Harris and colleagues[1] conclude that there is preliminary support for the safety and efficacy of psilocybin for treatment-resistant unipolar depression. This finding is important because more effective pharmacological treatments with acceptable side-effects are urgently needed for patients suffering from depression. We support the limitations the authors have pointed out about the study population and trial design. We also recognise the paucity of well-designed trials in psychiatry that are based on the principles of clinical pharmacology. Nonetheless, the study raises several crucial questions regarding its pharmacological aspects. At our institute, we apply the so-called Question-based Drug Development (QBD)[2] approach in the design of trials with innovative CNS drugs, which has enabled us to guide the development of various new CNS drugs along a rational path in the past 25 years. Essentially, the QBD approach requires reliable answers to six crucial questions to understand the pharmacological effects of CNS drugs, as illustrated below for psilocybin.

(1) Does psilocybin or its active metabolites reach the site of action? Psilocybin is administered orally, after which it is systemically absorbed, distributed across the blood–brain barrier and, at the same time, metabolised and excreted.[3] Additionally, psilocybin is a prodrug and is converted to the biologically active psilocin. Because the authors do not expand on these issues in their study, it is uncertain how psilocybin's pharmacokinetics relate to mood-elevating pharmacodynamic properties.

(2) Does psilocybin cause its intended pharmacological or functional effects? Psilocybin is thought to exert its primary pharmacological action through $5HT_{2A}$ receptor ($5HT_{2A}R$) agonism. To verify whether psilocybin actually has central serotonergic effects, establishing the effect of psilocybin on validated biomarkers for serotoninergic stimulation, such as cortisol and prolactin release[4] and pupil dilatation,[5] could be informative.

(3) Does psilocybin cause undesired pharmacological effects? Information about in-vitro receptor binding affinity or preclinical experiments with psilocybin is not provided, so it is unclear whether psilocybin has off-target or secondary pharmacological effects that might cause clinical side-effects or raise safety issues in patients with depression. Also, abuse potential after prolonged exposure is not addressed.

(4) Does psilocybin have beneficial effects on the disease or its clinical pathophysiology? $5HT_{2A}R$ agonism has been linked to enhanced cognitive flexibility, associative learning, cortical neural plasticity, and putative mood improvement in animals. Because these functional processes could be involved in the pathophysiology of depression, it might be useful to evaluate whether psilocybin has such functional effects in a population of patients with depression. Alternatively, the neuroimaging data that are yet to be presented might, therefore, provide interesting findings in terms of neuronal network biomarkers.

(5) What is the therapeutic index of psilocybin? The rationale for the selected doses is unclear because no previous dose-ranging has been done. Also, the relationship between psilocybin's presumed favourable mood-enhancing effects and toxic CNS effects remains obscure. Therefore, the presented clinical adverse effects might have been the result of unintended toxic CNS concentrations, which actually might have attenuated psilocybin's potential effects on mood.

(6) How do the sources of variability in response to psilocybin in patients with depression affect its application? Variability relating to both pharmacodynamic (such as population characteristics in terms of depression or tolerance due to previous antidepressant use) and pharmacokinetic (such as absorption, clearance, and gender) issues should be identified, to understand differences between individuals in terms of response or the occurrence of side-effects.

In our opinion, future trials with psilocybin in patients with depression will benefit from the QBD approach. After all, such a systematic approach is expected to yield information that would facilitate understanding of psilocybin's pharmacodynamic effects in relation to its pharmacokinetics, and as a consequence, increase the reliability of data generated in trials with patients.

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