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GUEST EDITORIAL

Subsyndromal delirium in old age: conceptual and methodological issues

Delirium is a cognitive disorder characterized by acute onset, fluctuating course, altered level of consciousness, inattention, disorganized thinking, disorientation, memory impairment, and perceptual and motor disturbances (American Psychiatric Association, 2000; World Health Organization, 2010). It occurs in hyperactive, hypoactive, or mixed forms in up to 42% of older hospital inpatients (Siddiqi *et al.*, 2006) and 70% of older long-term care residents (McCusker *et al.*, 2011). In both settings, delirium is independently associated with poor outcomes (Siddiqi *et al.*, 2006; McCusker *et al.*, 2010; Witlox *et al.*, 2010).

Both DSM-IV-TR and ICD-10 diagnostic criteria for delirium require the coexistence of symptoms from multiple domains (American Psychiatric Association, 2000; World Health Organization, 2010). It is common, however, for older people to display one or more symptoms of delirium without having the full syndrome (Rockwood, 1993; Kiely *et al.*, 2003). The occurrence of such symptoms has been labeled as subsyndromal delirium (SSD) (Levkoff *et al.*, 1996).

The existence of SSD is controversial. Some investigators claim that SSD may be a clinically important condition that falls on a continuum between no symptoms and full delirium, perhaps a marker for underlying medical conditions (e.g. infection, drug toxicity) not severe enough to cause full delirium (Levkoff *et al.*, 1996; Cole *et al.*, 2003). Others argue that distinguishing subsyndromal presentations from full delirium is not "clinically practical given the fluctuating course of delirium, as clinical manifestations may range from normality through subsyndromal to full syndromal delirium in a matter of hours" (Blazer and van Nieuwenhuizen, 2012).

To date, evidence for the existence of SSD is inconclusive. On the one hand, two studies of the course of SSD have reported that episodes of SSD appear to occur independently of full delirium, last for 1–133 days, and often end in recovery but often recur (Tan *et al.*, 2008; Cole *et al.*, 2012a). On the other hand, a systematic review of the studies of SSD has reported significant unexplained heterogeneity in the results of studies of prevalence, incidence, and some risk factors that may undermine the credibility of the findings of these studies (Cole *et al.*, 2012b).

Only further research will advance knowledge and determine whether or not SSD is a clinically important condition. To advance knowledge, such research must wrestle with six conceptual and methodological issues and try to avoid teleological reasoning and research design. These issues include the following: the types of symptoms of delirium required for the diagnosis of SSD, the number of symptoms required for diagnosis, the relationship of the symptoms present to full delirium, the measurement of the symptoms of delirium, prevalent versus incident SSD, and the selection of patient populations. Each of these issues is outlined below.

Types of symptoms of delirium

To date, three studies (Levkoff *et al.*, 1996; Cole *et al.*, 2003; Liptzin *et al.*, 2005) have defined SSD as the presence of one or more symptoms of delirium; the symptoms were inattention, altered level of consciousness, disorientation, and perceptual disturbances. Five studies (Marcantonio *et al.*, 2002; Bourdel-Marchasson *et al.*, 2004; Tan *et al.*, 2008; Leonard *et al.*, 2009; Cole *et al.*, 2011) have defined SSD as the presence of one or more Confusion Assessment Method (CAM) core symptoms of delirium; the CAM core symptoms were acute onset and fluctuation, inattention, disorganized thinking, and altered level of consciousness. Three studies (Ouimet *et al.*, 2007; Ceriana *et al.*, 2010; Skrobik *et al.*, 2010) have defined SSD as the presence of one to three symptoms of delirium on the Intensive Care Delirium Screening Checklist; the symptoms included altered level of consciousness, inattention, disorientation, hallucinations or delusions, agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbance, and symptom fluctuation. One study (Meagher *et al.*, 2012) has defined SSD as a severity score of 8–15 on the 13-item severity scale of the Delirium Rating Scale-98 (DRS-98); the severity scale includes disturbances in sleep–wake cycle, perception, thought form and content, affect, language, motor activity, orientation, attention, short- and long-term memory, and visuospatial ability. Finally, one study (Trzepacz *et al.*, 2012) has defined SSD

using a type of cluster analysis of the 13 severity items and two diagnostic items of the DRS-98. SSD was intermediate in severity between no symptoms and full delirium, but its phenotype was more like delirium; proposed criteria for SSD include acute change from baseline, thought disorder, disorientation to time and place and mild disturbances in sleep–wake cycle, inattention, and navigating in one's surroundings.

Of note, differences in the prevalence and incidence of SSD cannot be attributed to the diagnostic criteria used (Cole *et al.*, 2012b). Only one study has compared prevalence rates of SSD using two different sets of diagnostic criteria and reported little difference in the rates (Voyer *et al.*, 2009). The reason for the above findings may be that, despite differences in diagnostic criteria between studies, the symptoms that most frequently identify SSD are the same in all studies: to wit, two studies report that SSD was identified most often by the symptom of inattention (Cole *et al.*, 2003, 2011) and this symptom is common to all sets of diagnostic criteria.

Number of symptoms of delirium

Most studies of SSD have defined SSD by the presence of one or more symptoms of delirium, or two or more symptoms; consequently, it is difficult to evaluate the frequency or significance of the presence of one versus two versus three symptoms. That being said, three studies have compared the frequency of SSD defined by the presence of one versus two to three Confusion Assessment Method (CAM) core symptoms of delirium (Kiely *et al.*, 2003; Dosa *et al.*, 2007; von Gunten and Mosimann, 2010); and one study has compared the frequency and outcomes of SSD defined as the presence of one or more versus two or more CAM core symptoms (Cole *et al.*, 2011). Although the evidence is limited, it appears that the more the symptoms required for SSD diagnosis, the lower the prevalence and incidence rates and the poorer the outcomes.

Relationship of symptoms present to delirium

When SSD was described by Guainerio in 1517 (Diethelm, 1971), "... he emphasized that a predelirious period ... can be recognized which ... may not lead to full delirium." Similarly, Lipowski (1990) described a "prodromal phase ... in which patients had one or more symptoms of delirium (decreased concentration and ability to think, restlessness, anxiety, irritability, drowsiness, hypersensitivity to stimuli, nightmares) that never progressed to full DSM-defined delirium."

Many authors, however, have not distinguished between symptoms that do or do not progress to delirium (Kiely *et al.*, 2003; Marcantonio *et al.*, 2005; Dosa *et al.*, 2007; Voyer *et al.*, 2009; von Gunten and Mosimann, 2010). DSM-IV-TR recognizes "subsyndromal presentations ... with some but not all of the symptoms of delirium" and recommends that such presentations be coded as Cognitive Disorder Not Otherwise Specified (American Psychiatric Association, 2000). More recently, the DSM-V Neurocognitive Disorders Workgroup has discussed whether to add SSD as a subcategory of delirium in parallel with a new category, mild neurocognitive disorder (Jeste, 2010). Notably, neither DSM-IV-TR nor the DSM-V Workgroup distinguishes between subsyndromal presentations that do or do not progress to delirium.

Whether or not SSD occurs independently of delirium is a critical issue for research. Many symptoms of delirium appear to occur before and after episodes of delirium, at least in some populations (Cole *et al.*, 2012c). If the definition of SSD does not exclude symptoms that occur immediately before or after episodes of delirium, it may not be possible to distinguish the risk factors, course, and outcomes of SSD from those of delirium. If the definition of SSD excludes symptoms that occur immediately before or after episodes of delirium, it may be possible to distinguish the risk factors, course, and outcomes of SSD from those of delirium and investigate the possibility of a continuum of acute neurocognitive disorder in older people.

Of note, in 12 studies that excluded SSD progressing to delirium, the combined prevalence of SSD was 23% (95% CI = 9%–42%); the combined incidence was 13% (95% CI = 6%–23%); risk factors were older age, dementia, more cognitive and BADL impairment, admitted from an institution, increasing severity of medical illness, vision impairment, and more co-morbidity; outcomes (i.e. cognitive and functional decline, increased length of hospital stay and increased rates of admission to long-term care institutions, and death) were poor (Cole *et al.*, 2012b). In five studies that did not exclude SSD progressing to delirium, the reported prevalence of SSD ranged from 11.9% to 51%; the median rate was 39.5%. Two of these five studies reported risk factors similar to SSD not progressing to delirium and one reported outcomes similar to SSD not progressing to delirium. Notably, none of the five studies reported the proportions of subjects with SSD that did or did not progress to full delirium. Although the evidence is limited, it appears that the inclusion of subjects with SSD

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that may progress to delirium increases prevalence substantially but may not change risk factors or outcomes.

Measurement of symptoms of delirium

To date, the following four different instruments have been used to identify SSD: the Delirium Symptom Interview (Albert *et al.*, 1992), the Confusion Assessment Method (Inouye *et al.*, 1990), the Intensive Care Delirium Screening Checklist (Bergeron *et al.*, 2001), and the Delirium Rating Scale-98 (Trzepacz *et al.*, 2001). There do not appear to be consistent differences in the frequencies, risk factors, or outcomes of SSD when these different instruments are used (Cole *et al.*, 2012b), perhaps because a relatively small set of symptoms (e.g. inattention, disorganized thinking) identify most cases of SSD and are common to most of the instruments. Although the evidence is limited, the instrument(s) that best measure the small set of symptoms relevant to the detection of SSD are likely to be the most useful.

As yet, there is little consensus on the duration or frequency of measurement required to detect SSD. In published studies, the period of observation ranges from 5–180 days, median 7–8 days; when the period of observation has involved more than one assessment, the frequency of assessments has ranged from thrice per day to weekly, median daily (Cole *et al.*, 2012b).

Prevalent versus incident SSD

Prevalent SSD can be defined as a diagnosis of SSD at the time of first assessment. Incident SSD can be defined as a diagnosis of SSD following one or more assessments with no symptoms of delirium. Because prevalent SSD may represent the end of a resolving episode of delirium or even persistent symptoms of delirium (Cole, 2010), inclusion of prevalent cases in studies of SSD may preclude the study of SSD, independent of delirium.

Selection of patient populations

The prevalence and incidence of delirium can vary enormously by type of population selected (e.g. community, emergency room, medical inpatients, surgical inpatients, nursing home residents) and the frequency of dementia in the population selected (McCusker *et al.*, 2011). Risk factors for delirium tend to be similar among medical and surgical populations but may be different among nursing home populations (McCusker *et al.*, 2011). Outcomes seem to be uniformly poor across all populations studied, perhaps worse among those with dementia (McCusker *et al.*, 2001). Because findings will probably be similar for SSD, it may be important to consider the populations selected to study SSD.

Conclusion

What is SSD? What is the clinical significance of SSD? Does SSD occur independently of delirium? Is SSD a marker for underlying medical conditions not severe enough to cause delirium? Is SSD a clinically important condition requiring medical attention? Or does SSD reflect only the fluctuating nature of delirium and the fact that infrequent assessments of symptoms of delirium miss the diagnosis of full delirium? To answer these questions, further research must grapple with six conceptual and methodological issues and try to avoid teleological reasoning and research design. The issues include the following: the types and number of symptoms of delirium required for the diagnosis of SSD, the relationship of the symptoms present to full delirium, the measurement of the symptoms of delirium, enrolment of prevalent versus incident SSD, and the selection of patient populations. Research that satisfactorily addresses these issues may advance knowledge of SSD.

Conflict of interest

None.

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