Age of onset and timing of treatment for mental and substance use disorders: implications for preventive intervention strategies and models of care

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Purpose of review

To provide an update of the recent studies on the age of onset of the major mental illnesses, with a special focus on the prospects for prevention and early intervention.

Recent findings

The studies reviewed here confirm previous reports on the age of onset of the major mental disorders. While the behaviour disorders, and certain anxiety disorders, emerge during childhood, most of the high prevalence disorders (anxiety, mood and substance use) emerge during adolescence and early adulthood, as do the psychotic disorders. Early age of onset has been shown to be associated with a longer duration of untreated illness and poorer clinical and functional outcomes.

Summary

Although the onset of most mental disorders usually occurs during the first three decades of life, effective treatment is typically not initiated until a number of years later. Although there is increasing evidence to suggest that intervention during the early stages of a disorder may help reduce the severity and/or the persistence of the initial or primary disorder and prevent secondary disorders, additional research is needed into appropriate treatment for early stage cases as well as the long-term effects of early intervention, and to appropriate service design for those in the early stages of a mental illness. This will mean not only the strengthening and re-engineering of existing systems but also, crucially, the construction of new streams of care for young people in transition to adulthood.

Keywords

age of onset, duration of untreated psychosis, early intervention, mental disorders, prevention, treatment delay

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Introduction

Age of onset is a key clinical epidemiological variable, which has only recently become the focus of major study and interest. It is critical, as Kessler *et al.* [1] pointed out, firstly because it enables us to calculate the projected lifetime risk of disorder and secondly in capturing the topography of onset so that primary prevention, prevention of secondary disorders and early intervention strategies can be targeted in an efficient, timely and cost-effective manner. We have lacked solid data to draw this map and epidemiologists have been forced to rely upon two problematic sources: firstly, retrospective reports from community-based surveys, typically of an incomplete range of disorders, and, secondly, retrospective measures of treated incidence samples, which even for psychotic disorders are known to be incomplete. Certainly for the mood, anxiety, substance use and personality disorders, in which treated incidence and prevalence are low as a proportion of the total, age of onset data ascertained this way is of uncertain accuracy. The age of onset approach has surprised both researchers and policy makers in showing that the full lifetime risk for mental disorders approaches 50%, meaning that mental ill-health is a reality most of us will increasingly have to confront either in ourselves and/or in our families. This review provides an update of the recent studies of age of onset and especially those which relate onset to the prospects for prevention and early intervention. For psychotic disorders, this involves special attention to treatment delay and early quality of care, whereas in other domains a three-way focus upon maximizing treated incidence, reducing delay and enhancing early quality of care is necessary. Timing of onset across the lifespan and its relationship with treatment delay will also be considered. Finally, the implications for preventive and early intervention will be discussed.

Age of onset

The emerging cartography of age of onset, with 75% of incident cases emerging by age 25, has revealed that the

patterns for the mental and substance use disorders are virtually the mirror image of those seen in the chronic physical disorders [1,2]. This prompted Insel and Fenton [3] to characterize mental disorders as the chronic diseases of the young. With the decline of infectious diseases and other physical threats of earlier eras, at least in developed countries, the mental disorders have been revealed as the major contributor to the burden of disease in young people [4–7]. They also appear to be increasing in incidence [8,9]. Children in critical developmental stages and young people on the threshold of adult life have much to lose, as does society as a whole, from the neglect of this issue. More precise understanding of how and when disorders emerge is therefore urgently required. Let us consider the recent data concerning the major groupings separately and also, where possible, look for common patterns and sequences.

Mood and anxiety disorders

In their earlier review, Kessler *et al.* [1] used data from World Mental Health surveys to report the age of onset distributions of high prevalence disorders, including the mood, anxiety and substance use disorders. The results of these studies indicated that, while some anxiety disorders have a median age of onset within childhood (particularly phobias and separation anxiety), most of these high prevalence conditions typically emerge during early adolescence and early adulthood.

There have been a handful of population surveys of the prevalence, course and age of onset of high prevalence disorders since the review by Kessler *et al.* [1]. The National Comorbidity Survey Replication-Adolescent Supplement (NCS-A) [10••] reported prevalence and onset data on 10 123 adolescents in the USA using a modified version of the Comprehensive International Diagnostic Interview (CIDI). Anxiety disorders were the most common (31.9%), followed by behaviour disorders (19.1%), mood disorders (14.3%) and substance use disorders (11.4%). Approximately 40% met criteria for more than one class of disorder and the overall prevalence for any disorder with severe impairment and/or distress was 22.2%. The median age of onset for anxiety disorders was 6 years, 11 years for behaviour disorders, 13 years for mood disorders and 15 years for substance use disorders. However, given that the upper limit of the sample was censored at 18 years – therefore excluding not only the young adult onsets, which are considerable for mood and substance use disorders in particular, but also the onsets over 25 years – these figures must be interpreted cautiously in terms of defining the span and focus of prevention and early intervention efforts, which must extend from childhood through to the mid-20s at least.

Key points

- Age of onset is a critical variable in orienting our focus for prevention, early intervention and the architecture and design of mental healthcare.
- Most disorders emerge prior to the age of 25 years, through a cascade of stages with initial clinical syndromes resolving, evolving or collecting additional dimensions, often termed 'comorbidity'.
- Better understanding of the transition from mild, transient symptoms to onset of persistent disorder based on prospective community samples assessed from early in life is required.
- Treated prevalence remains low for most disorders, and treatment delay is increased for cases with onset earlier in life; coverage, quality and timing are critical foci for reducing the burden of mental ill-health to our societies.
- Scaling up of mental healthcare yet with a heavy weighting to the under-25s is urgently required and needs to involve a strong focus on adolescents and emerging adults as well as younger children.

Major epidemiological studies of depression in China [11] and the incidence and patterns of depressive and anxiety disorders in Germany [12••] have also recently been reported. In the Chinese sample ($n = 5201$ adults) [11], the mean age of onset of major depression was 30.3 years, which, although somewhat higher than the age of onset reported across Western surveys, is still broadly within the early adult range. The German study involved a prospective, longitudinal follow-up (over 7–10 years) of 3021 participants aged 14–24 years at baseline assessment. Consistent with the review by Kessler *et al.* [1], the age of onset distributions of anxiety varied according to the type of disorder, with social and specific phobias typically emerging during childhood, compared with general anxiety disorder and panic disorder, which characteristically emerged in adolescence and early adulthood. The latter pattern of onset was similarly observed for depressive disorders [12••].

Several studies have examined correlations between the age of onset of depression and the course or nature of illness, with an earlier onset associated with more chronic illness [13], a greater number of depressive episodes among women, but not men [14•], and longer episode duration, increased suicidality and need for hospitalization [15]. Of particular concern from an early intervention perspective, the latency to treatment initiation was found in one study to be significantly longer in those with childhood (mean = 12.9 years) and adolescent onset (mean = 6.3 years) compared to adult-onset depression (mean = 2.4 years) [15]. Given the well documented adverse outcomes associated with prolonged duration of untreated illness in psychosis [16], this finding underscores

the need for far greater early identification and intervention in emerging depressive disorders [17]. Clues to earlier recognition come from the Oregon Adolescent Depression Project [18], in which the risk of transition from subthreshold depression to major depression was estimated to be 67% by their early 30s in a sample of 225 adolescents. The survival function was linear, so the risk persisted from baseline in adolescence through young adulthood. Although subthreshold symptoms alone were a potent source of risk, this risk was enhanced by a range of additional variables, including female sex, greater severity of baseline depression, medical symptoms at baseline, history of anxiety or suicidal ideation and family history. These findings were similar to those found by Cuijpers *et al.* [19] in adults in primary care. We also know from recent research that intervening with subthreshold symptoms in adolescents is effective in reducing the risk of full-syndrome depression [20].

There have been several studies seeking to explore the pattern and significance of the onset of bipolar disorder [21–23,24••]. All studies utilized large samples, ranging from 1369 [22] to 3658 [23] patients. Three samples involved multicentre samples of convenience, which were recruited to clinical trials of other studies of bipolar disorder. The US studies tended to show earlier onsets and the presence of a large very early onset group [23]. Earlier onsets in all studies showed greater severity and other defining clinical characteristics. The UK study used mixture analysis to show that the distribution of the ages of onset comprised a mixture of three normal distributions, with a mean age of onset of 18.7, 28.3 and 43.3 years, respectively [22]. The clinical characteristics of these groups differed significantly. All of these studies, however, were retrospective and were not even first episode samples, so the results must be interpreted with caution. Tijssen *et al.* [24••] took a different perspective, sampling adolescents ($n = 1395$) between 14 and 17 years and following them up for up to 10 years. They found much higher incidence rates of hypomania and mania than in other clinical studies, and this supports the findings, derived from what appears to be an extension of the same sample, of Beesdo *et al.* [12••], who reported much higher rates than expected of both unipolar and bipolar mood disorders in adolescents and young adults. Tijssen *et al.* [24••] also found that only 38% of those experiencing mania and 13% of those experiencing hypomania accessed mental healthcare and, contrary to conventional wisdom, nearly two-thirds of both groups failed to develop subsequent episodes of depression. The authors concluded that experiencing (hypo)manic symptoms is a common adolescent phenomenon that infrequently predicts (current) mental healthcare use. However, the study was unable to determine what proportion of those who failed to access care actually needed it or would have benefited from it. The study shows the value of prospective community samples in understanding the onset of disorder and that in future the onset of bipolar disorder can be best elucidated by studying the pathway from nonpathological behavioural expression to dysfunction and need for care. This is the approach that may bear more fruit across the diagnostic spectrum, including psychotic disorders.

Substance use disorders

Epidemiological studies have consistently shown that prevalence of alcohol and drug use and abuse increases with age during adolescence and peaks in early adulthood. A report from the New Zealand Mental Health Survey ($n = 12\,992$) [25] details for the first time the onset and lifetime use of drugs and alcohol for all adult ages in that country. Onset curves for each substance are published and the median age of onset in each cohort was always lowest for alcohol, then cannabis, then opioids and then cocaine. The authors concluded that interventions to prevent or delay the onset of drug use need to occur before or during adolescence. Palmer *et al.* [26] followed a community-based twin sample of 1733 drawn from across the adolescent age range (12–18) into early adulthood with around 5 years separating the two waves of the study. There was an increase in lifetime prevalence of substance use disorders, of which alcohol was the most common, followed by nicotine and cannabis, from about 9 to 31%. Incidence and precise age of onset are difficult to determine from this type of study, though they do suggest generalized and specific risk pathways for substance use disorders.

A similar community follow-up survey of 43 093 adults [27] conducted by the National Institute of Alcohol Abuse and Addiction performed two sets of interviews 3 years apart. Earlier age of onset of drinking markedly increased the risks of alcohol dependence during follow-up, of 'driving under the influence' and of unintentional harm to self or others. Jackson [28•] reports on the characteristics of progression through early drinking milestones in a very large treated sample ($n = 3331$) in the Drug Abuse Treatment Outcome Study for Adolescents (DATOS-A) of adolescents with substance use disorders. They describe the phenomenon of 'telescoping', in which adolescents progress rapidly through the milestones to alcohol dependence and emphasize the need for detection and effective interventions for this subgroup at especially high risk. A range of other recent studies [29–35] have examined aspects of the early course of drug, alcohol, inhalant abuse and dependence, reporting clinical and sociodemographic risk indicators for progression, some of which appear to be stage-specific. The preventive and clinical utility of this new knowledge, however, remains unclear from these studies, which nevertheless tend to stress the value of early intervention during adolescence and emerging adulthood.

Psychotic disorders

Disorder-specific estimates of age of onset distributions for the affective and nonaffective psychotic disorders have not been separately reported in any of the World Mental Health surveys because of the under-representation of these cases in surveys. In their earlier review, Kessler *et al.* [1] used studies that either establish the treated incidence of psychosis in a well defined catchment area [36] or that observe onsets in long-term prospective general population cohorts [37,38]. According to these studies, the majority of psychoses manifest in the third decade of life, with a median in the early 20s and a narrow interquartile range, as for the impulse-control disorders and some anxiety disorders, and in contrast to the mood disorders [1]. Although schizophrenia usually manifests in the age range of 15–35 years, these estimates of the median age of onset may be biased downwards because these studies lacked information on the incident cases of schizophrenia at greater than 30 years. There has been one long-term prospective general population cohort study [39•] and one study utilizing data from the Danish Psychiatric Central Register [40] that reported age of onset in schizophrenia, including cases up to the age of 70 and above, since the review by Kessler *et al.* [1].

The Lundby Study [39•] analysed the incidence of schizophrenia and other psychotic disorders in the Lundby population over a 50-year period by comparing male and female age at onset, overall incidence rates and age-specific incidence rates. The male median age at onset for schizophrenia (22 years) was lower than that for female patients (46 years). The authors concluded that differences in incidence between the sexes in this 50-year follow-up may indicate psychotic disorder-delaying mechanisms in female patients, or different causes of psychosis in male and female patients. In the Danish registry study [40], two cohorts were established by linking data from the Danish Civil Registration System with data from the Danish Psychiatric Central Register, which covers all incident cases of schizophrenia from 15 to 71 years. The authors estimated the sex-specific and age-specific incidence rates of schizophrenia for people aged up to 71 years. The median age at onset for men and women was 27 and 29 years, respectively. It is difficult to reconcile these somewhat divergent findings; however, these studies that cover most of an individual's life span suggest that the median age of onset of schizophrenia for men is in the late 20s and for women is in the mid-30s.

There is meta-analytic evidence that younger age at onset of schizophrenia is associated with a positive family history for psychosis [41•] and that the age of onset of psychosis for cannabis users is 2.7 years younger than for nonusers [42•]. Studies conducted in minors recruited from child psychiatric settings have emphasized a relationship between the age of onset of schizophrenia and the course of illness, with earlier onset (before 18 years of age) possibly associated with a more chronic form of the disorder (for reviews see [43,44]), and more severe cognitive deficits [45]. These findings support the view that severity of the disease process may be associated with different ages at onset. However, as early onset and adult-onset patients are usually treated in separate clinical services, the notion that outcome in early onset schizophrenia may be worse than in adult-onset schizophrenia is based on samples that are not drawn from the same population, and may therefore be subject to selection bias. The traditional reluctance of child and adolescent psychiatrists to assign severe psychiatric diagnoses to minors could contribute to an over-representation of more severely ill chronic cases [46]. This diagnostic reluctance, combined with a hesitancy to prescribe antipsychotic medication, inevitably increases the duration of untreated psychosis and may contribute to poorer outcome in people with earlier onset. A study by Norman *et al.* [47] that examined factors associated with treatment delay in first episode psychosis supports this view. In this study, younger individuals had significantly longer delays from initial service contact to the initiation of adequate treatment, especially antipsychotic medication, until relatively late in the course of their illness. The accumulated evidence supporting a relationship between delay in initiation of treatment and outcome [16] demands that such hesitancy, particularly in many child and adolescent mental health services, be reassessed. The finding that younger individuals with first episode psychosis experience significantly longer treatment delay, that is, the duration of untreated psychosis, as compared with individuals with adult onset has been confirmed by the recent studies [48,49].

The importance of timely treatment initiation has been further underscored by new data from the Treatment and Intervention in Psychosis (TIPS) project showing that early treatment had positive effects on clinical and functional status at 2-year [50] and 5-year follow-up [51] in first episode psychosis. These studies showed that reducing the duration of untreated psychosis has longer-term effects on the course of negative symptoms, depressive symptoms, cognitive symptoms and social functioning, suggesting the possibility of secondary prevention of these pathologies in first-episode schizophrenia. Intensive education campaigns directed towards the general public, schools and primary health-care services appear to facilitate early detection [52], although, when stopped, a reversal in help-seeking behaviour was observed with an increase in the duration of untreated psychosis.

Conclusion

Although the facts about the contribution of mental disorders to burden of disease speak for themselves, certain commentators have been more sanguine about the immediate prospects for shrinking this burden [53]. Estimates (limited by many assumptions) have been made of how much of this burden could be averted if current evidence-based treatments were delivered to people with mental disorders. It is asserted that the modest efficacy and effectiveness of the existing treatments puts a relatively low ceiling on the extent to which the burden can be reduced. However, this analysis puts insufficient weight on two key variables: coverage of cases (treated prevalence) and timing of treatment. If we draw the analogy with physical illness, in which we expect 80–90% of cases to gain access to care (contrast this with 38% for the mental disorders in Australia [54] and perhaps less in many other countries), and further that early diagnosis of potentially fatal or chronic illness should be at a premium, then the impact and burden of mental disorders may be able to be much more substantially reduced. This is a testable hypothesis. Cancer survival rates have been improved greatly by these approaches and also by refining and enhancing the delivery of existing treatments. A staging approach, such as developed in internal medicine, may be useful in psychiatry to guide research and system reforms [55].

Key strategies need to address these issues of access, quality, coverage, and system reform and expansion. Public education campaigns to improve mental health literacy and help-seeking are the first step to increase coverage and access [52,56]. Progressively scaling up the capacity of the health system, both the primary and specialist tiers of care, with liberal access, assertive mobile detection strategies for 'hard to reach' cases, and genuine integration of multidisciplinary and age appropriate care are achievable objectives. The topography of onset and impact of disorders means that, if we are going to shrink the avertable burden of mental disorders, reduce suffering and improve productivity across the critical adult years of life, we must build strong, stigma-free and effective systems of care for children and young people up to the mid-20s [5,57]. This means creating a novel youth mental health model, overlapping with, but discrete in culture and expertise from, systems for younger children and older adults [58]. This reform is gaining ground in Australia [4,5,59]. Prevention-oriented evidence-based programs for younger children are also critical [60–62]. Investment in this stage of life is essential to address the hard fact that treatment delay is much more likely to occur if the onset is in children or young people. Age of onset is a vital statistic to guide our future mental health policies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 361–362).

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