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Developmental Transitions to Psychopathology: Are there Prodromes of Substance Use Disorders?

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One of the conceptual difficulties faced by developmental psychopathologists is the plethora of terms for “things that predate the full manifestation of a psychiatric disorder.” We have causes, vulnerabilities, susceptibilities, antecedents, risk factors, exposures, precursors, sub-threshold syndromes, and, of course, prodromes, the subject of this Annual Review. So we must first be clear as to what the word “prodrome” means, and how it differs from other terms for predictors.

Merriam-Webster’s dictionary defines a “prodrome” as a “premonitory symptom of disease,” and “premonitory” as “giving warning.” Conflating these two, we define a prodrome as a “symptom or sign that gives warning that a disease is present prior to the full manifestation of that disease.” A review of medical dictionaries on the web shows consistent references to a prodrome as “An early symptom indicating the onset of an attack or disease”; “a premonitory clinical sign; a clinical sign indicating the onset of a disease”; “a symptom, often noted prior to monitoring and diagnosis that may signal the beginning of a disease”, or “the earliest phase of a developing condition or disease.”

(<http://medical-dictionary.thefreedictionary.com>). Wikipedia provides an example: “...a prodrome is an early non-specific symptom (or set of symptoms) that might indicate the start of a disease before specific symptoms occur. For example fever, malaise, headache and anorexia (lack of desire to eat) frequently occur in the prodrome of many infective disorders“.

There is an important objection to the “non-specificity” clause in the Wikipedia definition, because there are some highly specific prodromes. We are thinking here of, for instance, the auras of migraine and epilepsy. In both cases, these are actually symptoms of the pathological process underlying the disorders that appear before the most characteristic and florid symptoms (headaches and seizures respectively), but that sometimes occur without those more florid symptoms following. Indeed, medication in the aural phase of migraine is used to preempt the headaches. An intermediate example is the “bull’s-eye” rash of Lyme disease, which may or may not be observed in its characteristic form prior to the onset of the full disease. Interest in prodromes of psychiatric disorders has been revived recently by work to intervene at the prodromal phase of first-onset psychosis (reviewed in Olsen, 2005). The key point here is that a prodrome is consistently defined as a *manifestation of the disease itself*, but non-specificity is not a necessary part of the definition of a prodrome.

What is *not* a prodrome?

A prodrome is *not* a characteristic of the person with the disease. For instance, neuroticism cannot be regarded as being a prodrome of major depression unless we are willing to argue

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that the personality characteristic called neuroticism is an early form of depression, thus doing away with the distinction between “personality” and “disorder.” Here we see the distinction between prodromes and what are often referred to as “vulnerabilities.” Age at onset of drug use is a potent predictor of later abuse and dependence (Robins and Murphy 1967; Anthony and Petronis, 1995; Sung, 2004 #15974}, but as a characteristic of the individual rather than the disease it is ineligible for prodromal status on that ground.

A prodrome is also *not* a characteristic of the environment in which a person lives. Low occupational status may be a “risk factor” for cardiovascular disease (CVD) because it is associated with higher rates of CVD and predates the onset of CVD, but it is not prodromal to CVD because low occupational status is not a symptom of CVD.

A prodrome *cannot* be a “causal” agent of disease, because that would do away the distinction between causes and diseases (a prodrome is a symptom or sign of the disease itself). Negative life events may cause depression (Brown and Harris, 1978), but they are not prodromal signs of depression. Similarly, a prodrome is *not* an “antecedent” of a disease, because the disease must be present if the prodrome occurs.

In summary, a prodrome *is* a premonitory manifestation of the disease. It *is not* a characteristic of the individual or their environment, or a causal agent of the disease. A prodromal symptom may or may not continue to be manifest once the full disease appears. Conversely, the same disease may or may not manifest prodromal symptoms in different episodes.

Prodromes and Substance Use Disorders

This paper examines the concept of the prodrome as it applies to substance use disorders (SUD). By SUD we refer to the disorders included in the Diagnostic and Statistical Manual of the American Psychiatric Association, 4th Edition (DSM-IV) (American Psychiatric Association, 1994), including dependence on nicotine, and abuse of and dependence on alcohol, cannabis, and other illicit drugs, as well as abuse or dependence resulting from off-prescription use of medications such as sedatives. The DSM makes the distinction between abuse, referring to use that impairs the individual’s ability to function in one or more important area of life, and dependence, which includes physical damage and a lifestyle that is centered on obtaining and using the drug, or at least (as in the case of nicotine dependence), severely disrupted if the drug cannot be obtained. The chapter on mental, behavioral, and developmental disorders in the International Classification of Diseases (World Health Organization, 1987) has similar categories (harmful use, and dependence state) to indicate the clinical state of the patient (the other ICD clinical states, such as psychotic disorder and amnesic syndrome, will not be considered here as they are very rare in young people).

It is worth noting that the term “addiction” is considered by many authorities, including the Directors of NIDA and NIAAA, to be a more appropriate term than “dependence” (O'Brien et al., 2006). Physical dependence can occur in anyone taking medications that affect the central nervous system, and therefore produce symptoms of withdrawal when discontinued, “However, the adaptations associated with drug withdrawal are distinct from the adaptations that result in addiction, which refers to the loss of control over the intense urges to take the drug even at the expense of adverse consequences” (O'Brien et al., 2006) (p.764). In this paper we use “addiction”, where appropriate, as equivalent to DSM-IV dependence.

Both the DSM and ICD make the distinction between harmful use or abuse and dependence. Implicit in this distinction are the ideas that (1) abuse precedes dependence; (2) abuse is less severe than dependence; (3) abuse increases the likelihood of dependence.(Feingold and

Rounsaville, 1995, Harford et al., 2005). Clearly we need to consider whether abuse constitutes a prodrome of dependence, but there are also other stages on the path to SUD whose claims to be prodromal need evaluation. These include exposure, use, heavy use and bingeing, as well as such variants as early use relative to population norms.

Then there is the literature on psychiatric precursors of SUD (reviewed in Costello, 2007)) from which it might be inferred that some early psychiatric disorders are prodromal to SUD. Research on endophenotypes has also been exploring aspects of personality and cognitive functioning that are characteristic of individuals with SUD, and which might be thought to be prodromal. We will examine the claims of each of these to be called a “prodrome”.

Exposure, use and heavy use

Exposure refers to the presence of psychoactive substances that the child or adolescent could theoretically use; cigarettes and alcohol in the stores, cannabis and cocaine on the street corner. As a candidate prodrome, exposure is easily dealt with. No-one would suggest that merely being exposed to adenoviruses (as we all are for much of the time) was a prodrome for a common cold, and it is similarly unreasonable to argue that the availability of substances represents a prodrome of addiction. Exposure is, however, a necessary “component cause” (Rothman, 1976) of SUD, because no-one can develop abuse of or dependence on a psychoactive substance without being exposed to it.

Exposure is also used in a slightly more sophisticated way in DSM-IV; exposures to volatile substances such as antifreeze are considered by DSM-IV as “toxins” if the exposure is accidental, and “inhalants” if used for the purpose of becoming intoxicated. However inhaling a toxic substance, whether intentionally or unintentionally, is not in itself a symptom of either abuse or dependence, and therefore not a prodrome.

Use of a psychoactive substance is also a necessary “component cause” of SUD. Is it, therefore, appropriate to regard substance use as a prodromal phase of later addictive behaviors? The answer is no. Neither DSM nor ICD defines *use* of a psychoactive substance, whether legal or illegal, as a *symptom* of a substance use *disorder*. The disorders are defined by sets of symptoms that accompany and result from the problematic use of the substance. For example, social drinking is not a symptom of alcoholism, but rather a normal behavior in many cultures. Alcoholic cirrhosis is a condition that sometimes results from alcohol use, but we do not think that anyone would claim that drinking alcohol in general should be regarded as being a prodromal stage of cirrhosis, so why should we regard alcohol addiction (a disease of a small proportion of alcohol users) in a different light? In both cases, alcohol use is a necessary cause of the disease, but not a symptom of it.

The only situation in which use could be seen as a prodrome of SUD would be use by someone who was previously addicted, and after withdrawing from the drug begins to use it again. In this case returning to use could be seen as a symptom of an already present disorder, which was non-symptomatic so long as the individual was not using the addictive drug. In this case the prodrome could not precede the onset of dependence, but would necessarily precede subsequent episodes; a rather anomalous use of the concept of a prodrome, and one that is in any case highly unlikely to have developed yet in children and adolescents.

Heavy use of alcohol or binge drinking are both, by current definitions, associated with greatly elevated risks for later alcoholism. But are they premonitory symptoms of *already present* alcohol addiction? Again, the answer is no. Most heavy drinkers and binge drinkers never meet DSM-IV criteria for alcohol abuse or dependence. For example, Hill et al. (Hill et al., 2000) used a longitudinal community study to compare outcomes at age 21 of three

types of binge drinkers (persistent from age 13 (3% of sample), onset at age 16 (4%) and onset at 18 (23%). They found that although each group of bingers had more alcohol and drug abuse or dependence at 21 than the non-bingers, the highest rate in any group was 43% (in the age 16 onset group). In this highest risk group, rates of high school completion, engagement in school or work, and family bonding were well over 50%. Contrast this with the situation in which one observes fever, lassitude, and a raised erythrocyte sedimentation rate in a previously well person. Here one believes that *something* is wrong (that some disease or other is present), but one does not know what that disease is. There is a prodrome of something, and perhaps time will tell what it is. In his review of the predictive value of heavy alcohol use, T.K.Li (Li et al., 2007) points out that heavy alcohol consumption increases the risk of many diseases, including cirrhosis of the liver, chronic pancreatitis, stroke, and certain cancers (Corrao et al., 2004). In the alcohol example, the risk of developing the disease (dependence) is higher, and we have a more specific behavior-outcome link, but we cannot conclude from the presence of either heavy use or binge drinking that “something is wrong.” Either may be seen as a *precursor* (something that predates and foretells in a probabilistic sense) of alcoholism, but not as a prodrome.

Alcohol is a legally available substance for adults, and it could be objected that the situation is different with illegal substances, where use and heavy use require additional (illegal) effort for their maintenance. There are three problems with this argument. First, most occasional and even heavy users never become addicts (Grant, 1996). Second, the distinction between prodrome and disorder becomes the arbitrary result of the legal status of particular substances. If the legal status of the drug changes, so does the prodromal status of illegal use. Third, it runs into a difficulty, shared with nicotine use, that heavy use may be the expression of the full disorder in itself. Over age 18 one may legally smoke a pack of cigarettes a day, but almost everyone who does so is nicotine dependent. In our society, is it not reasonable to assume that anyone who “wants” two or three hits of heroin a day is dependent upon it? In these cases, there seems to be little point in making the distinction between heavy use and addiction, and so the idea that heavy use is a prodrome of addiction is equally pointless.

Substance abuse: a prodrome of substance dependence?

A distinction enshrined in the separation of substance abuse and dependence is that of severity. Substance dependence was designed by the writers of DSM-IV to be a worse state than substance abuse (American Psychiatric Association, 1994) (p.182), although the symptom lists provided for abuse and dependence are non-overlapping. If the symptomatic requirements for substance dependence are independent of those for substance abuse, one could dismiss on logical grounds the possibility that the latter is a prodrome of the former. We believe that such a conclusion would be overly sophisticated. The reason is that the original formulation of the distinction between abuse and dependence was partly based upon the idea that abuse was indeed prodromal; that it was an earlier manifestation of the disease process that ended in dependence. It was also supposed that abusive behaviors would continue in the dependent state (American Psychiatric Association, 1994) (p.182), (much as oppositional defiant disorder was supposed to be a forerunner of conduct disorder). In other words, dependent individuals were supposed to be a subset of abusive individuals. In some people abuse would progress into dependence, whereas in others it would not. Note that we have already stipulated that progression to the pathological end state is not a requirement for a prodrome; one may have a bulls-eye rash without progressing to Lyme disease or a migraine aura without developing a headache. Nevertheless, the two are manifestations of the disease process.

There are three arguments that would support prodromal status for abuse, if substantiated: (1) Abuse is more common than dependence? (2) Abuse precedes dependence in time; (3) The symptoms of abuse are less severe than the symptoms of dependence

1. ***Is abuse more common than dependence?*** The answer may vary by drug of abuse. A nationally representative survey of adults (the National Epidemiologic Survey of Alcohol and Related Conditions: NESARC) found that lifetime prevalence of drug dependence was about one-third that of drug abuse (abuse 7.7% (SE 0.2%), dependence 2.6% (SE 0.1%) (Compton et al., 2007). Furthermore, this was true for each age group, from 18 through 65+, despite lower lifetime prevalences with increasing age. However, using a mixed sample of clinic and community subjects, Ridenour and colleagues (Ridenour et al., 2003) found that, whereas a lifetime history of abuse was more common than a lifetime history of dependence for alcohol and cannabis, there was no statistically significant difference in the case of cocaine and opiates.
2. ***Does abuse precede dependence in time?*** Ridenour and colleagues (Ridenour et al., 2003) found a similar variation among drugs when asking whether abuse preceded dependence. In this retrospective study the predominant pattern was for alcohol and cannabis abuse to precede dependence by more than one year, but this was not the case for cocaine and opiates; abuse and dependence typically occurred in the same year, and only in 33% (opiates) and 26% (cocaine) of cases was abuse reported more than a year before dependence. On the other hand, across the four types of SUD examined in this study, between 14% and 20% of patients reported the onset of drug dependence more than a year before that of abuse. By definition, a prodrome must be an early manifestation of a disease. In the study by Ridenour and colleagues (Ridenour et al., 2003) between 9% (alcohol) and 20% (cannabis) of subjects with dependence met criteria for abuse *after* they first met criteria for dependence, so at least for this sizable minority abuse could not be described as prodromal.
3. ***Are the symptoms of abuse less severe than the symptoms of dependence?*** Item Response Theory methods have been used to test the hypothesis that dependence symptoms are more characteristic of a severe disorder, and abuse symptoms of a mild disorder. Hartman et al. (Hartman et al., 2008) looked at this question in relation to cannabis in over 5,000 adolescents from a mixture of community and clinical sources. They found that two symptoms of abuse (legal and social/interpersonal problems) were associated with the highest level of severity, and two dependence symptoms (tolerance and withdrawal) with the lowest level. This reflects earlier findings in adults by Teesson et al (Teesson et al., 2002). Martin et al. (Martin et al., 2006) reported similar findings for alcohol and cannabis from a clinical sample of adolescents. Using retrospective data from 372 adult clinical patients, looking at alcohol, cannabis, and cocaine symptoms, Langenbucher and colleagues concluded that for all these disorders “there is no clear relationship between the identity of a criterion as denoting abuse versus dependence on the one hand and the severity of the pathology it measures on the other.” (Langenbucher et al., 2004) (p.76). The NESARC survey of over 43,000 American adults (18 and over), used Item Response Theory to determine whether abuse and dependence symptoms were on a continuum of severity (Saha et al., 2006). The criterion information curves identified dependence criteria (e.g. drinking larger amounts or for longer periods than intended, withdrawal, tolerance, desire or unsuccessful efforts to quit or control drinking) that were well represented among the mildest criteria, and abuse criteria (e.g. hazardous use) that tapped the more severe range of the continuum. Thus far, based on studies of both children and adults, in clinical

and community samples, the assumption of greater severity of dependence symptoms is not supported by the evidence. This argues against abuse as a prodrome of dependence.

Preceding psychiatric disorders

There can be no doubt that substance abuse and dependence are very often preceded by a variety of psychiatric and behavioral problems (Costello, 2007). For example, in a special edition of *Drug and Alcohol Dependence* on this topic, several papers showed prediction from conduct disorders (Fergusson et al., 2007, Gibbons et al., 2007, Pardini et al., 2007, Costello et al., 2007, Wittchen et al., 2007). Prediction from ADHD became negligible after controlling for conduct disorders (Fergusson et al., 2007, Pardini et al., 2007, Costello et al., 2007, Wittchen et al., 2007), while prediction from emotional disorders varied across studies (Fergusson et al., 2007, Pardini et al., 2007, Costello et al., 2007, Wittchen et al., 2007). Developmental processes also played a role. Conduct disorder (though, interestingly, not oppositional defiant disorder) predicted early-onset drug use and SUD, but ceased to be predictive in the later teens, once drug use became “normative” (Sung et al., 2004). Among the groups of adolescents at particularly high risk of beginning to use drugs, the first step to SUD, are early maturing girls, who are also at increased risk of behavioral problems (Magnusson et al., 1985, Costello et al., 2007). We hope, however, that the arguments presented so far have made it apparent that these psychiatric precursors cannot be regarded as prodromes of SUD. They certainly are *risk factors* for substance problems, and may be *outcomes* of substance problems (e.g., Brook et al., 1998), but they are not prodromes. Depression and conduct disorder, for instance, share no symptoms in common with substance abuse and dependence, so they cannot, by definition, be prodromes of SUD.

Extraversion, reward dependence, risk taking and other personality constructs

Personality characteristics such as extraversion, reward dependence and risk taking have long been associated both concurrently and prospectively with substance use problems (Block and Block, 1988, de Wit and Richards, 2004). Children who have poor ability to self-regulate as infants and later show deficiencies in executive functioning, are at increased risk for SUD (Tarter, 2002, Giancola and Mezzich, 2003). These, however, are characteristics of *individuals*, not characteristics of the disorder. Risk-takers may be more likely to try drugs and to become addicted to them (Kelly et al., 2006, Comeau et al., 2001), but being a risk-taker is not a symptom of substance abuse or dependence. Such personality characteristics may, therefore, be regarded as being “risk factors,” “susceptibilities,” or “vulnerabilities” for substance problems, but they are not prodromes.

Discussion

The areas briefly reviewed above demonstrate that we are a long way from identifying prodromal symptoms for adolescent (or adult) SUD. On logical grounds alone most of the identified precursors cannot be prodromes. The most promising place to look was along the developmental pathway supposed to run from use to abuse to dependence. But the data have shown no clear consensus about the relationship between abuse and dependence; i.e., we do not yet have a clear definition of the end-state disease. So how could we possibly identify a prodrome?

So we have to look elsewhere to pick out children at high risk of developing a substance use disorder. There is no shortage of research to inform us, showing that genetic variation, personality characteristics, and psychiatric disorders, while not prodromes, nevertheless play a role in predicting SUD. Children who have drug abusing parents, especially a mother who uses drugs during pregnancy (Griesler and Kandel, 1998, Weissman et al., 1999) are born at

higher risk, which increases if they receive little monitoring from their parents and become involved in drug-using peer groups (Ennett and Bauman, 1993, Hoffmann et al., 2000). In addition, there are characteristics of the environment – “social capital” in the form of school and neighborhood qualities -- that can increase or decrease the likelihood of SUD (e.g., Guo et al., 2000, Hawkins et al., 1992).

Earlier, we made use of Rothman’s elegant presentation of the idea of “component causes” in medical research (Rothman, 1976). Rothman argues that for any disease there are likely to be several causal components. Rarely is one sufficient on its own, but it may form part of several causal clusters in conjunction with different sets of component causes. The factors touched on are clearly parts of one or more causal clusters. So far, however, we have failed to identify a single factor that can be called “prodromal”.

Despite our failure to find any, the idea of prodromes has considerable appeal; if one could be identified, future patients could be identified early, and treatment begun before the worst symptoms appeared. Since a prodrome is by definition an early phase of the illness itself, by the time it appears it will be too late for universal or high-risk prevention (National Research Council and Institute of Medicine, 2009), but there may be time for “indicated prevention” strategies (Gordon, 1983) to reduce the severity of the illness and prevent recurrence and residual disabilities. Therefore, there would be benefits to identifying prodromal symptoms of SUD.

In the meantime, the pattern of precursors that has emerged from the literature in recent years permits us to identify the points in the developmental trajectory of SUD that might be amenable to preventive interventions. This is not the place for a detailed review of these interventions (see National Research Council and Institute of Medicine, 2009, Toumbourou et al., 2007), but clearly treatment for parents, especially for pregnant women, has to be a priority. Training programs that support children’s developing powers of self-regulation (Posner and Rothbart, 2000) and parents’ ability to monitor their children (e.g., Spoth et al., 2002) can also help. Governmental interventions to reduce access to substances and enforce rules about underage sales have been shown to be effective with young people (reviewed in Cokkinides et al., 2006). If prevention fails, treatment programs for adolescents have had some modest success (Toumbourou et al., 2007). However, none of these interventions identifies prodromes or articulates an intervention specifically addressing a prodrome.

In summary, there is a lot of information – sociological as well as personal – that we can use to identify individual children at high risk for developing SUD, and plenty that can be done to help them. But at present we cannot hope to identify prodromal symptoms. To do so, we will need to learn a great deal more about the pathophysiology of SUD, particularly at the level of brain development (Volkow and Li, 2005).

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