AMPA receptor potentiating drugs, ampakines)[4]. mGlu5 antagonists have been tested in ASD associated with fragile X syndrome, and showed promise in a subgroup of patients[5]. GABAergic agents, such as the GABA-B receptor agonist arbaclofen (STX209), have shown some effect on irritability and social withdrawal in ASD children[6].

The peptide hormone oxytocin is important in social cognition and behavior. In ASD adults, acute intravenous administration of oxytocin reduced repetitive behaviors[7] and improved accuracy of recognizing emotions in speech over time[8]. Intranasal administration improved social cognition in children, adolescents and adults with ASD[9]. A vasopressin 1a receptor antagonist had some effect on speech recognition of emotions such as fear and lust in high-functioning ASD adults.

Insulin-like growth factor 1 (IGF-1) is important in central nervous system maturation, development and connectivity, that are perturbed in ASD. Studies in Shank-3 deficient mice that model Phelan-McDermid syndrome (PMS), which may be associated with some cases of ASD, indicated that IGF-1 may reverse structural changes in ionotropic glutamate receptors, functional synaptic plasticity changes, and excitation/inhibition imbalance. A clinical trial with recombinant human IGF-1 in PMS children showed improvement in social impairment and restricted behaviors[10].

Agents modulating the immune system have been tested in ASD. The immune response induced by the whipworm Trichuris suis ova has shown benefit on the repetitive behavior domain in adult ASD. Immunosuppressive and protein synthesis inhibiting drugs such as the mTOR inhibitor rapamycin have been shown to improve social deficits in some forms of ASD.

The alpha-7 nicotinic acetylcholine receptor (nACR) gene is associated with autism and ADHD. nACR drugs tested in clinical trials include mecamylamine, transdermally administered nicotine, and donepezil. Some alpha-7 nACR antagonists such as galantamine have shown promise in animal models and clinical trials.

Drugs modulating the cannabinoid system, such as cannabidiol, have been found effective in childhood epilepsy, and may be worth studying in ASD due to their anti-anxiety, anti-epileptic, immunomodulating and cognitive-enhancing effects and good safety. Interestingly, social reward and oxytocin induce release of endocannabinoids in nucleus accumbens. In ASD animal models, cannabidiol has some impact on social deficits, repetitive behaviors and irritability.

Complementary and alternative medicine (CAM) treatments have been tested in ASD. However, they are not strictly regulated and have not been studied in large-scale clinical trials. Therefore, their safety and efficacy is not well determined. CAM treatments may complement rather than replace proven therapies for ASD. Melatonin may be used for sleep disorders, omega-3 fatty acids for reducing repetitive behaviors and improving sociability. Vitamin B12 supplements are believed to protect against the oxidative damage in ASD. Curcumin, an active ingredient of turmeric, may be beneficial in ASD, perhaps owing to its anti-oxidant and anti-inflammatory properties. Probiotics such as yogurt may have effects on the gut microbiome and on pro-inflammatory cytokines that may play a role in the pathogenesis of ASD.

In summary, the enormous heterogeneity in ASD complicates development of new pharmacotherapies. Personalized treatments are desirable, and studies of syndromal orphan populations may accelerate drug development. Design of future clinical trials needs to address patient stratification on the basis of biomarkers or etiology (for example, immune-inflammatory) and target populations stratified by clinical symptoms.

New pharmacotherapies such as oxytocin/vasopressin antagonists, anti-inflammatory agents, IGF-1, drugs regulating excitation/inhibition balance, protein synthesis inhibitors, and microbiome-targeting drugs may be of particular promise. Existing drugs such as anticonvulsants, SSRIs and atypical antipsychotics may be beneficial in some patients. It is important to test the effectiveness of drugs in younger children who may benefit most from early intervention. The ultimate goal of ASD pharmacotherapy will be to match the treatment to the underlying molecular mechanisms in individual patients.

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Nonmedical use of prescription drugs in adolescents and young adults: not just a Western phenomenon

Nonmedical prescription drug use, generally defined as use without a prescription or use for reasons other than what the medication is intended for, is a global concern, primarily driven by the high and rising phenomenon of nonmedical use of prescription opioids in young populations. Prescription drugs are legal and hence tend to be more easily available than most illegal drugs.

Nonmedical use merits particular attention given the high degree of abuse potential[1] and numerous ill-health consequences, that vary depending on the drug. Nonmedical use of prescription stimulants can lead to irregular heart rate, hypertension, cardiovascular system failure, stroke and seizures, while nonmedical use of prescription opioids can cause respiratory suppression and overdose[2]. Most of drug-related deaths worldwide are due to either prescription opioid or heroin overdoses. A recent review has illustrated worldwide increased rates of deaths from prescription opioids[3], with the exception of Australia. In Europe, prescription opioids account for three-quarter of overdose deaths, which represent 3.5% of total deaths among 15-39 year olds.

Nonmedical use of stimulants and prescription opioids among adolescents and young adults has also been linked to increased harmful use of other substances[4], reporting of psychiatric symptoms, psychiatric disorders and suicidal ideation[5].

Despite the undisputed worldwide concern, it is important to note the variability in the prevalence/patterns of nonmedical use of prescription drugs among young people. In the US, according to the 2014 National Survey on Drug Use and Health, past-year nonmedical use of prescription drugs (opioids, stimulants, tranquilizers and sedatives) was reported by 6.2% of 12-17 year-olds and 11.8% of 18-25 year-olds, mainly driven by nonmedical use of prescription opioids, which has remained stable in the past decade despite rising trends since the late 1990s. Data from the 2012 Canadian Alcohol and Drug Use Monitoring Survey showed that 4.9% of 15-24 year olds were past-year nonmedical users of the above cited prescription drug classes. Data from the 2013 Australian National Household Survey showed an increase in nonmedical use of prescription drugs since 1998, particularly among 14-19 year olds; the 2013 past-year estimates were 4% among 14-19 year olds, and 5.8% among 20-29 year olds. While comparability is hindered by the varying methodologies, definitions, and age categorizations, data clearly supports the global concern for the nonmedical use of prescription drugs among young vulnerable populations.

General household population data among young populations in other countries are not as readily available, but there is data from school-based and college-based surveys in Europe, Latin America, Asia and the Middle East. In Europe, data from 36 countries collected as part of the 2011 European School Survey Project on Alcohol and other Drugs showed that, on average, 6% of European school students (mean age of 15.8 years) reported lifetime nonmedical use of tranquilizers (data on other drug classes are unavailable).

Data on high school or university students from the Middle East or Arab world indicate that nonmedical use of prescription drugs warrants closer attention. In Beirut, Lebanon, past-year nonmedical use of any prescription drugs was 21.6% among private university students, and 10% among high school students. In both populations, prescription opioids were the drugs most commonly used nonmedically. In Saudi Arabia, a recent school-based survey showed a lifetime prevalence of 7.2% for the nonmedical use of any prescription drug.

In Brazil, the most recent national school-based survey, conducted in 2010, showed that the past-year prevalence of nonmedical use of prescription stimulants among middle/high school students in public and private schools was 1.6% and 2.2%, respectively. Only lifetime data on nonmedical prescription opioid use was collected (0.3% of all middle/high school students). One study from Southern China conducted in 2007-2009 revealed that 6% of the middle/high school students had tried any prescription medication nonmedically, mostly opioids, followed by cough medicine with codeine. A 2012 high school survey from Chongqing, China reported a lifetime prevalence of 11.3% for the nonmedical use of prescription opioids only. For comparison purposes, data from the 2015 US Monitoring the Future school and college-based surveys showed that 12.8% of 12th graders used any prescription drugs nonmedically.

It is important to shed light on important socio-demographic differences. College-based studies exclude significant proportions of minority or low socio-economic status young adults, who are at higher risk of developing a prescription drug use disorder once they start using the drugs. Evidence on gender differences among adolescents and young adults has been mixed: some studies have found no difference; others have found a higher prevalence in males or in females[6,7]. Early age of initiation of nonmedical use has been associated with higher likelihood of ill-health outcomes, including a higher probability of developing substance use disorders[8]. Individuals with previous nonmedical use of prescription opioids may be at greater risk of heroin use and heroin dependence[9]. Motives for nonmedical use also vary (i.e., to get high; to self-medicate), leading to the presence of several heterogeneous subgroups of nonmedical users that are at varying risks of other substance use[10].

Worldwide comparisons are hampered by the variations in the study methodologies, including definitions of nonmedical use or prescription drugs included. The impact is also different given the varied availability and cultural acceptance of the drugs worldwide. Prescription drug monitoring programs, recently implemented in the US, Canada and Australia, are not widely available globally and, where available, there is unevenness in how they operate. Today, the biggest challenge is balancing a country's need to make available prescription drugs to those in need (i.e., those with chronic pain) while simultaneously curbing diversion and nonmedical use. Pharmacists in some countries struggle between providing medical advice and service to those who cannot afford a doctor's prescription while meeting the requirements of their governmental regulations. Another challenge is controlling the top most reported sources of supply, including parents, doctors and friends, highlighting the need to target multiple sources simultaneously.

The greater "social acceptance" for using these medications (versus illegal substances) and the misconception that they

are "safe" may be contributing factors to their misuse. Hence, a major target for intervention is the general public, including parents and youth, who must be better informed about the negative consequences of sharing with others medications prescribed for their own ailments. Equally important is the improved training of medical practitioners and their staff to better recognize patients at potential risk of developing non-medical use, and to consider potential alternative treatments as well as closely monitor the medications they dispense to these patients.

The United Nations Office of Drugs and Crime is already assisting several governments in collecting epidemiologic data more efficiently as well as developing monitoring and training programs that ensure these drugs are available to those who need them while strictly avoiding diversion for nonmedical purposes.

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The concept of basic symptoms: its scientific and clinical relevance

The concept of basic symptoms originates from retrospective descriptions of the prodromal phase of schizophrenia, published in the first half of the 20th century and continuously developed through its second half[1]. It was not until the mid 1990s, however, that basic symptoms attracted a broad attention within two main lines of research: an empirical approach to early detection of psychosis[2] and a heuristic approach to define the Gestalt of schizophrenia by so-called "self-disorders"[3].

Basic symptoms are subtle, subjectively experienced disturbances in mental processes including thinking, speech, attention, perception, drive, stress tolerance, and affect[1,2,4]. Following training, they can be reliably assessed with a clinical interview from age 8 onwards using the youth and adult version of the Schizophrenia Proneness Instrument[5,6] (available at www.basicsymptoms.org). They have been reported in all stages of psychotic disorders, including prodromes and acute states of first episode and relapse, as well as residual states[1,2,4].

Basic symptoms are regarded as an immediate symptomatic expression of the neurobiological processes underlying psychosis and the earliest form of self-experienced symptoms – hence the term "basic". In contrast, attenuated and overt psychotic symptoms are assumed to develop later, as a result of poor coping with initial symptoms, such as basic symptoms, or stressors, when a vulnerable individual's protective mechanisms are overstrained[1,4]. With its focus on the emerging disorder, the concept of basic symptoms has been linked to a better understanding of the origins of psychoses, in particular schizophrenia, and to an improvement of their (early) diagnosis and treatment.

Initially, two criteria for the identification of basic symptoms were developed: cognitive-perceptive basic symptoms (COPER) and cognitive disturbances (COGDIS)[1,2,4]. COGDIS requires two of nine cognitive basic symptoms to occur at least once per week and is increasingly used as a clinical high-risk criterion in addition to ultra-high risk criteria[2,7]. The first meta-analysis comparing various clinical high-risk criteria found pooled conversion rates in COGDIS-defined samples of up to 61% at follow-ups of more than four years. Medium- and long-term pooled conversion rates of COGDIS samples were significantly higher than those of ultra-high risk criteria samples[7]. Thus, the European Psychiatric Association recommended ultra-high risk criteria and COGDIS to be used alternatively for psychosis risk assessment[7]. However, the presence of both COGDIS and ultra-high risk criteria appears to increase psychosis predictability compared to either criterion alone[2].

In spite of their neurobiological conceptual foundation, basic symptoms have only recently been considered in neurobiological studies of psychosis. Several correlates of these symptoms in psychotic and clinical high-risk individuals have been reported. These included changes in event-related potentials, neural oscillations, neurotransmitter systems, and large-scale networks as assessed with functional magnetic resonance imaging[4]. However, there is a need for further studies in clinical and non-clinical samples exploring the neurobiological correlates of individual basic symptoms and their relevance to the development of psychosis[4].

The basic symptoms concept has informed research on alterations of the very experience of the self as a core feature of schizophrenia[3,8]. Within this line of research, basic symptoms are an integral part of the so-called "anomalous self-experiences", "(basic) self-disturbances" or "self-disorders"[3]. Starting with E. Bleuler's characterization of schizophrenia as "a loss of unity of the personality", self-disturbances have always had a central role in the concept of schizophrenia, being explored by authors such as Minkowski and Blankenburg. Currently, alterations in self-disturbances, including the "development of an integrated sense of self" are believed to have common underlying neurobiological mechanisms[8]. Basic symptoms offer an empirical approach to test related hypotheses, such as perceptual incoherence or