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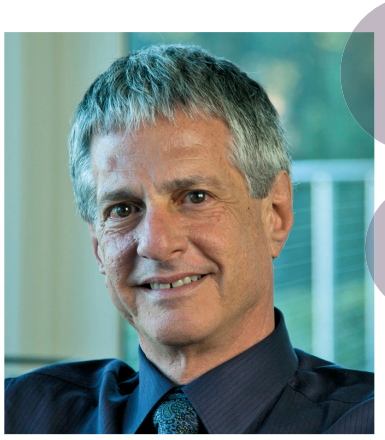
Substance Use Disorders in Crisis Settings

Engagement, Assessment, and Intervention Approaches



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Individuals with active substance use disorders (SUDs) who present to mental health crisis settings have often been regarded as "unwelcome visitors" who have come to the wrong place. Characterizations of at least some of these individuals (whether they present with substance use as the major complaint or with additional complaints such as suicidality, risk of violence, or active co-occurring psychiatric illness) by staff in many crisis settings are often negative.

Persons with active SUDs may not present in ways that fit our framework of how we can help. He or she may show up with symptoms or in situations that are clearly caused or exacerbated by substance use, but at the same time have no interest in receiving a referral for treatment. Another person may present with true desperation, but what he or she is asking for is not "psychiatric help," but rather a place to stay, a medication, or something else that we cannot provide. Individuals with active substance use may state that they are suicidal without having serious intent, or they may have substance-related symptoms that exacerbate—or obscure—the presence of psychiatric illness. Finally, these individuals may not fit either addiction or psychiatric settings—our usual set of resources—and may be misunderstood and unwelcome.

Since the late 1990s, best practice recommendations emphasize that individuals in crisis with active SUDs, and particularly those with comorbid psychiatric and substance use disorders, should be considered not only as "welcome" but also treated on a priority basis.

Because of a number of factors, including the opioid epidemic, the need to re-think our prioritization of "who is in crisis" and "who needs our help the most" has become more urgent in the past few years. It is critical that the most effective engagement and clinical practice protocols are utilized, especially for patients who have co-occurring medical, psychiatric, cognitive, or significant social challenges (eg, homelessness). Rather than encountering barriers to access and unwelcoming attitudes, these individuals must be prioritized and provided with an organized and effective crisis response.

STEP ONE: Welcoming practice

Implementing "welcoming practice" for individuals with active substance use requires clear policies and procedures that govern the expectations of behavior for all staff and requires monitoring and oversight by clinical and administrative leaders.[1]

Staff need clear instructions about how to treat individuals who may be engaging in behaviors that generate negative reactions. First, the person who needs help is welcomed and our intention to help is explained. The help we

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ACTIVITY GOAL

To goal of this activity is to provide a comprehensive, practical approach to working with individuals who are in active SUD crisis.

LEARNING OBJECTIVES

At the end of this CE activity, participants should be able to:

- Welcome individuals who present in crisis
- Develop guidelines for integrated longitudinal assessment
- Establish an environment of safety and stabilization
- Individualize disposition planning and continuity of care

TARGET AUDIENCE

This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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provide is immediate as well as continuing. The person is made to feel safe, and over time we connect the person with services that will help him progress toward achieving meaningful life goals.

Welcoming includes never using disparaging or disrespectful language, even when the individual is not listening. It also includes the ability to empathize with the person who may be displaying challenging or difficult behavior. For example, this might include a person who has frequent episodes of intoxication but continually refuses referral to addiction treatment. He is living a desperate existence and may feel hopeless about being able to get sober. He is at his wit's end and does not know how to get help. Or, it might be a person who has chronic pain, anxiety, depression, a history of trauma, and poorly managed opioid use presents with what might be considered "inappropriate" demands for pain medication. This individual is someone whose life is falling apart, is at high risk for a lethal outcome but who has no safe or easy way to ask for help other than by requesting medications for pain.

It is important to reframe our perceptions and change our approach. Incorporate a welcoming message in your routine instructions for preparing your patients for what to do when they are in crisis after hours. Let them know that they are always welcome to call for help (whether calling you directly or calling the crisis service that you use for back up), even if they have been using substances. For instance, you can say: "Call for help as soon as possible, so we can help you be safe and stable. It is helpful if you can call for help before you use substances, but substance use is never a barrier to calling for help. Our goal over time is to help you to develop the skills you need to manage these challenges successfully . . . but for right now, it is important that we meet you exactly where you are."

STEP TWO: Rapid integrated longitudinal assessment

Arbitrary barriers to assessment

Once the individual with active substance use is welcomed for care, we begin the assessment immediately and proceed with a thorough structured and integrated approach to learn best how to be helpful in the moment. Many crisis programs have adopted rules that automatically delay crisis assessment of anyone who is actively "under the influence," often requiring that the blood alcohol level is below the legal limit of intoxication before crisis assessment can begin.

There is no rational clinical basis for having this rule. Under no circumstances should any provider of crisis services have a formal or informal policy that creates barriers to treatment for individuals with substance use.[2] Note the following language in the current crisis management protocol utilized in Arizona.

> ***Assessment begins at the point of clinical contact, regardless of the client's [sic] clinical presentation. Initiation of assessment should not be made conditional on arbitrary criteria such as length [sic] of abstinence, non-intoxicated alcohol level, negative drug screen, absence of psychiatric medication, and so on.***[3]

The assessment of individuals in crisis needs to begin immediately. If the person is too intoxicated to communicate clearly, we still need to assess for any immediate risk to safety based on medical or behavioral lack of control (including risk of inadvertent falls or self-injury), as well as to rapidly access any available collateral information. The assessment of the individual begins with welcoming engagement and messages of safety and support while the person is intoxicated and proceeds to a more detailed discussion as soon as the person can carry on a conversation.

Some individuals will have their best and most honest conversations when their alcohol blood level is 0.2 (or when they are high on some other substance); some may not. That is part of the assessment. In addition, if the person presents with intoxication and complaints of suicidality, he is treated as potentially more at risk of self-harm than someone who is equally suicidal but sober; it is essential to evaluate the level of suicide risk when the person is intoxicated, not just hope that the person will "change his mind" when intoxication clears.

Guidelines for integrated longitudinal assessment

A frequent barrier to rapid and effective crisis intervention is the belief that assessment cannot proceed quickly because substance use may result in symptoms that mimic those of psychiatric illness. Although there are instances where this may occur, it should never delay beginning the assessment to quickly establish as much information as possible and proceed accordingly.

Guidelines for appropriate diagnostic assessment of individuals with an SUD in crisis have been described in the literature, and include the following:

1. Identify the person's goals and request for help, to establish connection and reinforce hope.

2. Using the framework of an HPI (history of presenting illness), identify the person's most recent stable baseline, before the current crisis. Gather information from the patient as well as collateral information from a partner/relative, previous treaters, and health records that include baseline mental status and mental health treatment, health status, SUD treatment efforts during the most recent period of abstinence or controlled use. Carefully describe—chronologically—the sequence of events proceeding from the last period of stability to the current presentation.

The Case Vignette illustrates an approach that rapidly provides information that identifies diagnosis, current baseline treatment, and recommended interventions, even though the patient may still be under the influence.

CASE VIGNETTE

John has a long history of schizophrenia and alcohol use disorder. He lives in supported housing by himself, supported by his case management team who see him one to two times a week. At baseline he is managed on several medications, but even on his best day he has auditory hallucinations, and finds that using alcohol provides him with short-term relief. His team has been working hard to help him reduce or eliminate his alcohol use, and he recognizes that the short-term relief is often followed by exacerbations of voices.

John recently started on oral naltrexone and reports better control of craving. However, today he went out with some friends who offered him alcohol and an unknown substance described as "synthetic marijuana." John reports that, "The alcohol didn't do much for me, but the other stuff made me feel pretty good for a while. Then, all of a sudden, the voices got real loud and I started to panic."

Alternatively, the same approach might yield a different story and imply a different solution. For example, John reports that he stopped his medication three weeks ago and has been responding to increased voices by trying to control them with more and more alcohol and drugs. He is very ambivalent about going back on medication but also knows that the alcohol and drugs are not working. He is scared and feels out of control.

In most cases, history (from multiple sources) will establish the probable diagnosis, baseline state during previous periods of abstinence, reasons for the immediate decompensation or crisis presentation, and recommended intervention. In some instances, assessment may need to be extended, either because more collateral information is needed and/or the person may not be initially coherent enough to provide accurate information.

3. Be cautious about diagnostic assumptions. Many crisis settings utilize the diagnosis of "Substance-induced disorder" for almost every patient who presents with active substance use that has an impact on symptoms. This is very misleading. In most instances, persistent mental illness (which may be exacerbated, or at times masked, by substance use) can be identified by history. A diagnosis of "substance-induced psychiatric disorder" requires that the psychiatric symptoms were initiated only in response to significant substance use and clear up completely within 30 days after substance use is discontinued. Substance-induced psychiatric disorder therefore is a diagnosis of course—not cause—and should be utilized cautiously; whether the symptoms will in fact clear up quickly is often uncertain. Overuse of "substance induced disorder" may lead to underdiagnosis and undertreatment of persistent disorders that may be present already or that may be just beginning.

4. Use urine screening judiciously as one piece of potentially corroborating information, along with self-report, collateral reports, and the person's clinical presentation. Note that some substances (eg, synthetic cannabinoids, fentanyl) may not be detectable in the urine screen, and, conversely, urine screening may be positive without a commensurate understanding of quantity of use. Each crisis setting should be aware of what substances do not appear in

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its urine screen, as well as the threshold for a positive result, and what medications (including over the counter use) may lead to false positives.

5. Identify any immediate risks due to intoxication, withdrawal, suicidality, violence, or exacerbation of mental illness/medical conditions that require emergent intervention.

6. Once immediate safety is established, assess carefully to determine what is the best next step to engage the individual in ongoing services that will help him increase stability and make progress over time.

STEP THREE: Establish immediate safety and stabilization

Each crisis setting must have clear protocols and medical/nursing resources for addressing intoxication and withdrawal. Note however that even programs with minimal medical support can still safely manage most episodes of intoxication safely. The level of withdrawal severity, measured by tools such as the CIWA-Ar (Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised) for alcohol or COWS (Clinical Opiate Withdrawal Scale) for opioids, determines intervention protocols in the behavioral health crisis setting.[4,5] In more severe cases, the results help to clearly delineate referral to an emergency medical setting.

The determination of level of care for medical detoxification is based on assessment of the patient's history and risk factors for withdrawal (previous history of seizures, DTs, etc) as well as withdrawal severity: What happened the last time you experienced withdrawal? How do you see this time as being the same or different as what happened before?

Establish behavioral control

Many crisis settings assume that individuals who are intoxicated are inherently riskier in their behavior than those who are not. This is not true. While active substance use may lead people to be more impulsive in general, each person must be assessed and addressed based on individual need and presentation. Often, welcoming the individual with kindness, respect, and helping him feel safe and comfortable, in a place where the experience can be resolved with support will lead to resolution of the intoxication without escalation. By contrast, individuals who are actively intoxicated may become more belligerent if staff are being unduly confrontational or disrespectful.

Protocols for using medication for behavior management

Individuals who are displaying symptoms of psychosis or agitation when under the influence of substances, or withdrawing from substances, commonly respond to the same medications that can be used with individuals who are not using substances, with the following cautions.

Be alert for agitation due to early signs of withdrawal. For example, individuals may start to display alcohol withdrawal before their blood alcohol level is zero, and the consequent agitation may respond quickly to medication (eg, benzodiazepines) to alleviate those symptoms. Similarly, individuals with opioid use disorders may attempt to minimize their degree of addiction, but then become extremely uncomfortable as they go into withdrawal and require specific interventions.

Adopt and utilize established protocols for emergency management of agitation. The American Association for Emergency Psychiatry Guidelines for the Pharmacologic Treatment of Agitation provides simple guidance for responding to agitation that is substance related compared with nonsubstance related.[6]

Identify and address withdrawal symptoms

Managing and treating withdrawal symptoms that may emerge during a behavioral health crisis evaluation or crisis intervention (in any level of care) requires different protocols than the management of agitation per se. Each crisis program should therefore develop simple protocols for consistent management of alcohol withdrawal, sedative-hypnotic withdrawal, opioid withdrawal, and withdrawal from other categories of substances (cannabinoids, hallucinogens, stimulants, etc).

Do not automatically assume that all persons in withdrawal must be referred to a "detox" program. Most individuals with mild to moderate withdrawal (from any substance) can be managed successfully in a psychiatric crisis program that can prescribed medications. Even if a higher level of care is needed, withdrawal management should be initiated as soon as possible. While opioid withdrawal can be relieved with clonidine, it is recommended that crisis programs are permitted to provide buprenorphine and are able to perform buprenorphine inductions. Although withdrawal symptoms may not be as specific biologically for other substances, they can lead to significant discomfort and agitation and should be managed consistently and symptomatically.

Naloxone administration

Crisis settings are first responders and are increasingly likely to have exposure to individuals with life threatening overdose. In a psychiatric crisis setting, an individual may have hidden opioids and use them after admission or obtain opioids from a visitor (even with reasonable search protocols). All crisis settings must have naloxone available and capacity to administer naloxone in the event it is needed.

STEP FOUR: Individualized disposition planning and continuity of care

A common frustration of crisis providers is that individuals who present with significant substance use are routinely referred for abstinence-expected treatment (in a detoxification or addiction treatment program), even if that is not an appropriate match for what the individual wants, needs, or is ready for. This results in the person refusing the recommendation, being discharged to no service, and recidivism or accepting the referral and then not following through, leaving AMA (against medical advise), or being administratively discharged. These results are neither clinically appropriate nor a good use of resources.

Crisis standards of care developed by Balfour and colleagues[7] include quality indicators that look at issues of repeated psychiatric crisis visits (including SUDs) as an improvement opportunity. The authors recommend that all crisis settings emphasize individually matched engagement and continuity of care (not just referral for an episode of sobriety) as markers of success. As with other chronic conditions, this approach is unlikely to achieve perfect remission, so much as to create the ability for engagement that will lead to improvement and stabilization over time.[8]

The ASAM (American Society of Addiction Medicine) Criteria for patient placement —the gold standard for addiction service matching—helps connect individuals for whom typical addiction treatment programs are not appropriate to other levels of care including proactive community-based case management.[9] These models have demonstrated success for high risk individuals who cannot or will not engage in more conventional services. Crisis services should establish the following guidelines for disposition planning.

Individualized patient needs

Care should be individualized to each person's crisis presentation and request for help, and should not involve referral for abstinence-expected services. The ASAM criteria can guide connection to levels of care that may include continuing community-based outreach. At the same time, it is important to remember that individuals who present with psychiatric issues (suicidality, psychosis) are at increased risk if there is comorbid substance use.

Tools such as the LOCUS (level of care utilization system) 20 reinforce that additional comorbidity for individuals who demonstrate safety risk can lead to a higher level of care than might be indicated for the MH presentation alone.[10]

Prioritize engagement of high risk individuals

Individuals with substance use disorders (including those who present with frequent intoxication, requesting a place to stay or stating they are suicidal in order to get a bed), should be treated as high-risk and need to be engaged immediately. The crisis system should have a clearly demonstrated mechanism for providing crisis follow up for up to 90 days for these individuals. Intramuscular naltrexone is likely to be of benefit as well as crisis case management. Engaging individuals with severe alcohol use disorders in some level of community-based services may help them gain control even if at first they continue to use substances.[11]

The importance of engaging high-risk opioid users

Individuals who present with unmanaged pain, requests for opioids or for higher dosages of opioid, or other indications of potentially risky or lethal

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opioid use should be prioritized for engagement. These individuals need crisis consultation and to be involved in some level of continuity of service, including initially with the crisis provider if necessary. A plan needs to be in place that helps them to manage pain and/or opioid use disorder with or without mental health and trauma issues, while minimizing risk of eventual overdose.

Medication-assisted treatment

The crisis system must consider medication-assisted treatment for opioid use disorders (with or without co-occurring mental illness), including buprenorphine induction, initiation of naltrexone, and rapid connection to same day or next day methadone initiation. Around the country, state Medicaid agencies and Medicaid managed-care organizations are initiating 24-hour access to buprenorphine induction in the public crisis system.

Collaboration with addiction treatment providers

For persons who need and want a referral to abstinence-based addiction services, the crisis system maintains strong partnerships with the continuum of substance use disorders service providers, including provision of proactive consultation and welcoming offers of instant crisis response. This will encourage addiction treatment providers to be more willing to accept patients who may be psychiatrically or medically unstable, because they know the crisis provider will support them if something goes wrong and will be available to help with any patient who has an acute mental health crisis.

Tips for outpatient practitioners

If your patient presents in crisis with active substance use, it is important to remember to take a leadership role in developing the follow-up plan after the crisis episode is resolved. Treatment providers are usually ideally suited for helping patients learn from the crisis episode, incorporate information that might help them make better decisions about substance use, decide whether they need additional help, and develop skills to ask for help before becoming intoxicated. It is important not to overreach by demanding abstinence as a condition of continued treatment, or assuming that the patient has "learned his lesson." The crisis involving substance use is usually a continuing journey, in which the treatment provider helps the patient make progress one small step at a time.

References

1. Minkoff K, Cline CA. Inspiring a welcoming and hopeful culture. In McQuistion HL, Sowers WE, Ranz JM, Feldman JM, Eds. *Handbook of Community Psychiatry*. New York: Springer; 2012.
2. Lukens TW, Wolf SJ, Edlow JA, et al. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med*. 2006;47:79-99.
3. Cenpatico Integrated Care. Crisis Protocols: Pima County 2018. file:///C:/Users/NTimoshin/AppData/Local/Microsoft/Windows/Temporary%20Internet%20Files/Content.Outlook/EJ7B83EF/Pima%20Crisis%20Protocol%202018%20Final%20V1.0.pdf. Accessed December 7, 2018.
4. Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84:1353-1357.
5. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale. *J Psychoact Drugs*. 2003;35:253-259.
6. Wilson, MP, Pepper D, Currier GW, et al. The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. *West J Emerg Med*. 2012;13:26-34.
7. Balfour ME, Tanner K, Jurica PJ, et al. Crisis Reliability Indicators Supporting Emergency Services (CRISES): a framework for developing performance measures for behavioral eealth crisis and psychiatric emergency programs. *Comm Ment Health J*. 2016;52:1-9.
8. McCormack RP, Hoffman LF, Wall SP, Goldfrank LR. Resource-limited, collaborative pilot intervention for chronically homeless, alcohol-dependent frequent emergency department users. *Am J Public Health*. 2013;103(Suppl 2):S221-S224.
9. American Society of Addiction Medicine. *ASAM Criteria: Treatment Criteria for Addictive, Substance-Related and Co-occurring Conditions*, 3rd ed. Washington, DC: ASAM; 2013.
10. American Association of Community Psychiatrists (AACP): LOCUS: Level of Care Utilization System for Psychiatric and Addiction Services: Adult Version 20. December 2016.
11. Collins SE, Saxon AJ, Duncan MH, et al. Harm reduction with pharmacotherapy for homeless people with alcohol dependence: protocol for a randomized controlled trial. *Contemp Clin Trials*. 2014;38:221-234. ❐

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Use of Psychodrama

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Reference

1. McLeod S. Erik Erikson's Stages of Psychosocial Development. 2018. https://www.simplypsychology.org/Erik-Erikson.html. Accessed December 10, 2018. ❐

First Episode Psychosis

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erythrocytes than controls. In FEP, neutrophils were significantly negatively associated with gray matter volume (β=-0.17), and significantly positively associated with cerebrospinal fluid volume (β=0.19). None of the blood cell types were associated with white matter volumes. Higher neutrophils were also associated with greater PANSS total (β=0.17) and positive subscale (β=0.17) scores, including specific items for hallucinations, suspiciousness/persecution, disturbance of volition, and preoccupation. Findings were not confounded by antipsychotic or other psychotropic medication exposure. Importantly, neutrophil counts remained stable 2 years after the initial blood assessment, which argues against an acute infection contributing to these findings. In controls, none of the blood cell counts were associated with gray matter, white matter, or cerebrospinal fluid volumes.

The researchers concluded that theirs is the first study to show associations between blood neutrophil counts, psychopathology, and brain volumes in psychosis. These findings were specific to patients with FEP, who also had higher blood neutrophils than controls. The pattern of reduced gray matter volume was generalized all over the brain rather than localized. Findings further support a role for immune system dysfunction in schizophrenia. Strengths of the study include the relative large sample size, and consideration of multiple potential confounding factors, including antipsychotic medication and acute infection. Limitations of the study include the observational design, use of multiple MRI scanners, blood and imaging were not performed on the same day, and absence of data on anti-inflammatory medications, inflammatory diseases, and sleep problems.

The bottom line

Findings indicate that neutrophil counts are associated with brain volumes and psychopathology in FEP, supporting a role for immune dysfunction in the pathophysiology of this disorder.

References

1. Miller BJ, Goldsmith DR. Towards a Schizophrenia Immunophenotype: Progress, Potential Mechanisms, and Future Directions. *Neuropsychopharmacol*. 2017;42: 299-317.
2. Cannon TD, Chung Y, He G, et al, for the North American Prodrome Longitudinal Study Consortium. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biol Psychiatry*. 2015;77:147-157.
3. Fillman SG, Weickert TW, Lenroot RK, et al. Elevated peripheral cytokines characterize a subgroup of people with schizophrenia displaying poor verbal fluency and reduced Broca's area volume. *Mol Psychiatry*. 2016;21:1090-1098.
4. Jickling GC, Liu D, Ander BP, et al. Targeting neutrophils in ischemic stroke: translational insights from experimental studies. *J Cereb Blood Flow Metab*. 2015;35:888-901.
5. Vita A, De Peri L, Deste G, et al. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry*. 2012;2:e190.
6. Nunez C, Stephan-Otto C, Usall J, et al. Neutrophil count is associated with reduced gray matter and enlarged ventricles in first-episode psychosis. *Schizophr Bull*. August 10, 2018; Epub ahead of print. ❐