ANGER EVERYWHERE: ADDRESSING AGITATION IN PSYCHIATRIC DISORDERS

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Learning Objectives

• Identify the hypothesized neurobiological bases of agitation in a variety of mental illnesses

• Integrate treatment of agitation into the care of patients with various psychiatric issues
Patient Assault on Clinician

- Escalation to violence
- Harm to patient, other patients, and/or staff
- Coercive measures including restraint, seclusion, or involuntary medication
- Director of the NIMH Division of Adult Translational Research, Dr. Fenton was caring for a psychotic patient in his private office
- Was beaten to death by the 19-year-old male patient

Patient Assault on Clinician

A National Institute of Mental Health (NIH) administrator and expert in the diagnosis of schizophrenia was beaten to death in his office by a patient.

A psychiatrist in Virginia was killed in his home office by a patient.

A physician at Johns Hopkins Hospital was shot by a man who was distraught about his mother’s care. The man then killed his mother and himself.

So...How Prevalent Is This?

- Sadly, these events are only a glimpse of the overall problem.
- The true incidence is difficult to measure, for the following reasons:
  - Information collected from a variety of sources using different methodologies for gathering data.
  - Lack of reporting protocols and mechanisms.
  - Failure to report nonphysical violent incidents (e.g., verbal abuse, threats, and stalking).
- Between 2011 and 2013, the majority of injuries and assaults at work occurred in the healthcare and social services settings.
- 23,540–25,630 annual assaults/injuries with 70–74% occurring in the healthcare and social service setting.
- For healthcare workers, assaults comprise 10–11% of workplace injuries involving days away from work, compared to 3% of all private sector employees.

Healthcare workers face significant risks of job-related violence

While under 20% of all workplace injuries happen to healthcare workers...

Healthcare workers suffer 50% of all assaults.

Source: Bureau of Labor Statistics
What can cause agitation?

• Psychiatric conditions:
  • Schizophrenia spectrum disorders, bipolar disorder (especially manic and mixed states), personality disorders, anxiety disorders, major depressive disorder, autism spectrum disorder, delirium

• Substance use and/or intoxication

• General medical conditions:
  • Dementia, encephalitis, meningitis, brain trauma, thyrotoxicosis, hypoglycemia, hypoxia, seizure, toxic medication levels

• If no psychiatric history is present, a general medical condition should be suspected until ruled out

Risk Factors for Aggressive/Violent Behavior

- multiple psychiatric diagnoses
- younger age
- depression
- gender
- homelessness
- childhood abuse
- longer duration of untreated psychosis
- cognitive dysfunction
- sensory and motor function impairments
- substance abuse
- child conduct disorder
- treatment nonadherence

Increased Risk of Violent Behavior

histories of violent behavior

low education
Healthcare Settings at Risk for Violence

- Hospitals
- Nursing Homes
- Community Care Facilities
- Small Mental Health Clinic
- Field Work/Home Visits

U.S. Department of Labor Occupational Safety and Health Administration OSHA 3148-06R 2016
Escalation of Agitation to Aggression: Neural Circuits Involved in Aggressive Behavior

- **A**: amygdala
- **H**: hippocampus
- **Hy**: hypothalamus
- **NA**: nucleus accumbens
- **PFC**: prefrontal cortex
- **S**: striatum
- **T**: thalamus

- Lack of top-down inhibition of impulses and cruel and insensitive thoughts
- Delusions, hallucinations, drug rewards, motivation
- Provocation
- No fear conditioning
- Excessive fear conditioning
Assessing Agitation*

- Patient interview
- Interview with family, friends, regular outpatient care providers
- Medical history
- Psychiatric history
- Substance use history
- Social and family histories
- Mental status examination

*See Appendix for useful assessment tools
Bottom-Up Drive and Top-Down Brake

- **Bottom-Up Drive** from limbic areas:
  - GO
  - STOP

- **Top-Down Brake** from cortical areas:
  - GO
  - STOP

Go and stop arrows indicate the direction of control signals in the brain.
The Agitation/Impulsivity Network: Top-Down Brakes Balance Bottom-Up Sensory and Emotional Drives
Top-Down Inhibition Prevents Overstimulation of the Agitation Network: Motor Output
Mechanisms of Aggression in Different Psychiatric Disorders

Deficient cortical brake

STOP

Deficient limbic activity

Psychopathic aggression
ASPD

Impulsive aggression
ADHD

Psychotic aggression
Schizophrenia
Schizoaffective disorder
Bipolar disorder
SUD

Impulsive aggression
PTSD
Borderline personality disorder
SUD

Excessive limbic drive

GO

Striatal hyperactivity

GO

Stahl SM, Morrissette DA. Stahl's Illustrated Violence; 2014.
Neurotransmitter Systems Involved in Aggression

Stahl SM, Morrisette DA. Stahl's Illustrated Violence; 2014.
Case 1: Stalking

- Intern at a public hospital
- Patient was homeless man in his 50s
- Patient requested a physical exam, due to discharge from genitals
- Patient engaged in inappropriate sexual behavior during the exam
- While the patient was stopped, the patient requested to remain in the same hospital and began stalking
- Stalking occurred for months, strange things happened to my car, he brought me gifts
- Wrote “together forever”
Case 2: Violence

• Medical Director at Stanford Hospital
• Patient who had a violent history was informed by a resident that he had to have a special diet, because he was diabetic
• He verbally threatened the resident
• He broke a chair, ripped wooden trim off the wall with nails, broke several computers, threw one at the ward clerk, smashed all the picture frames, and left a hole in the wall
• Calmed down immediately when security arrived
• Transferred to another hospital that had experience with him
• Considered pressing charges, but local law enforcement was reluctant
• Number of years later, this patient was in the hospital ER, and I told them about his history
• Threatened to “beat (me) to a pulp”
• Filed restraining order
## Patient vs. Setting-Related Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors from Patient</th>
<th>Setting-Related Risk Factor</th>
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<tbody>
<tr>
<td>Working directly with patients who have a history of violence, substance abuse, gang members</td>
<td>Poor environmental design of the workplace that may interfere with the employee’s visual information or escape from a violent incident</td>
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<tr>
<td>Transporting patients</td>
<td>Poorly lit rooms, corridors, parking lots, etc.</td>
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<tr>
<td>Working alone in a facility or in patients’ homes</td>
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<tr>
<td>Prevalence of firearms, knives, and other weapons among patients and their family/friends</td>
<td>Lack of means of emergency communication</td>
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<td>Working in neighborhoods with high crime rates</td>
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<tr>
<td>Organizational Risk Factors</td>
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<td>----------------------------</td>
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<tr>
<td>Lack of facility policies and staff training on how to manage escalating hostile and assaultive behavior from patients</td>
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<td>Working while understaffed, especially during mealtimes and visiting hours</td>
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<td>High worker turnover</td>
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<td>Inadequate security and mental health personnel on site</td>
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<td>Long waits for patients or clients and overcrowded, uncomfortable waiting rooms</td>
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<td>Unrestricted movement of the public in clinics and hospitals</td>
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<tr>
<td>Perception that violence is tolerated and will not be reported</td>
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</tbody>
</table>
Assessing Risk in Patients

The best predictor of violent behavior is a history of violence

Ask for more detailed information about patients with a history of assault

Try to have a friend/family member present for initial evaluation

Screen patient for weapons, and make sure they do not have access to weapons

Risk of patient becoming violent can stem from a variety of different diagnoses, and each will provide different information

Psychotic patient—notice nonverbal cues

Confused patient—talk to them and find out more

Be alert; be thankful/respectful to the patient

Violence isn’t always from anger: It may be from fear; look for signs of both

Teamwork is essential
## Evaluate and Ensure a Safe Environment

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<tbody>
<tr>
<td>Have the office set up so that there are not a lot of heavy objects (e.g., paperweights, etc.)</td>
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<tr>
<td>Ideally have two escape routes (two doors)</td>
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<td>Have an alarm button easily accessible</td>
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<tr>
<td>Have furniture that is made of safe material (not wood), and not easily picked up.</td>
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<tr>
<td>Wear lanyards for your badge that are choke-proof (magnetic or pop-beads)</td>
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<tr>
<td>Men—avoid neckties unless required</td>
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<tr>
<td>Women—jewelry with magnetic clasps, avoid long dangling earrings, have hair up or back</td>
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<tr>
<td>Closed-toe shoes that you can run in</td>
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</table>
**De-escalation Interventions**

<table>
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<tr>
<th>Action</th>
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<tbody>
<tr>
<td>Listen to the patient!! Make sure they know you’re listening/empathize</td>
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<tr>
<td>Paraphrase back to them in a neutral way</td>
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<tr>
<td>Can make it clear that you have heard them, even if they’re saying something that’s factually not true</td>
</tr>
<tr>
<td>Make sure they’re comfortable/minimize waiting time</td>
</tr>
<tr>
<td>Offer ways to calm them down (e.g., a cup of water, food, nicotine replacement, etc.)</td>
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<tr>
<td>Watch your environment and protect yourself (don’t put yourself in a physically vulnerable position)</td>
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<tr>
<td>Don’t “throw anyone under the bus;” this just puts them in danger</td>
</tr>
<tr>
<td>If a patient targets one clinician, try to generalize to the whole team</td>
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<tr>
<td>Stay calm</td>
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<tr>
<td>Go get help if needed</td>
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<tr>
<td><strong>Always</strong> tell the rest of the team what happened to alert others</td>
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</table>

Principles of De-escalation

• Respect personal space
• Do not be provocative
• Establish verbal contact
• Be concise
• Identify wants and feelings
• Listen closely to what the patient is saying
• Agree or agree to disagree
• Set clear limits
• Offer choices and optimism
• Have a back-up security team ready, in case of escalation
• Debrief the patient and staff

The Ideal Medication for Agitation

- Easy to administer
- Non-traumatic
- Provide rapid tranquilization without excessive sedation
- Fast onset of action
- Sufficient duration of action
- Low risk for side effects

- Currently available pharmacological treatment options are less than ideal

Oral vs. IM Formulations

- Oral formulations may not have a rapid enough onset of action
  - May require concomitant benzodiazepine
- IM formulations may be more traumatic for the agitated patient
- Newly developed inhaled formulation acts as rapidly as IM medication

Atypical Antipsychotics

- Generally recommended over conventional antipsychotics for acute agitation
  - Similar efficacy compared to conventional antipsychotics, with less risk of motor side effects
- Available in IM formulations
  - Aripiprazole*
    - Approved for acute agitation in schizophrenia and bipolar disorder
  - Olanzapine
    - Approved for acute agitation in schizophrenia and bipolar disorder
  - Ziprasidone
    - Approved for acute agitation in schizophrenia
- Ease of transition to oral or depot maintenance therapy

Clozapine

• Not recommended as a first-line treatment due to the risk of serious adverse effects (most notably agranulocytosis)
• However, clozapine has perhaps the greatest anti-aggressive properties
• Anti-aggressive properties are independent of effects of psychosis

Oral Atypical Antipsychotics for Acute Agitation

- Similar efficacy among aripiprazole, olanzapine, risperidone, quetiapine, and ziprasidone (and the conventional antipsychotic, haloperidol)

- May reduce agitation within 2 hours

- Adjunctive, fast-acting benzodiazepine may be required

Lurasidone

Brexpiprazole

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>BREX 2 mg</th>
<th>BREX 4 mg</th>
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</thead>
<tbody>
<tr>
<td>Socially useful activities, including work and study</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Personal and social relationships</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Self care</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Disturbing and aggressive behaviors</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
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</tbody>
</table>

Mean (SE) change from baseline

Conventional Antipsychotics

• IM chlorpromazine is generally not recommended as first-line

• Haloperidol
  • May cause neuroleptic malignant syndrome, QTc prolongation, and extrapyramidal symptoms (EPS), which may worsen agitation
  • Co-administration of lorazepam, promethazine, or diphenhydramine may lower risk of EPS
  • Use of haloperidol for agitation discouraged in a Cochrane review—atypical antipsychotics favored

Inhaled Loxapine

• Onset of action as quickly as 10 minutes after administration
• Approved for the treatment of agitation associated with schizophrenia and bipolar disorder
• EPS and akathisia are rare
• Dysgeusia (distorted sense of taste) most common adverse effect

Benzodiazepines

- May be excessively sedating
- Increased risk of falling due to coordination disruption and respiratory depression
- In patients with TBI, benzodiazepines can be disinhibiting
- Benzodiazepines can be inadvertently rewarding, causing an increase in agitated behavior
- Less EPS compared to conventional antipsychotics
- Clonazepam may escalate psychosis or agitation
- Intravenous diazepam may be effective, but IM diazepam not recommended
- Intranasal midazolam may be as fast-acting as IM benzodiazepines
- Caution with midazolam because it’s a respiratory depressant
- Recent Cochrane review suggests no clear advantage of adding a benzodiazepine to antipsychotic treatment

Recent advances in agitation management include:

- INP105 is an intranasal olanzapine that delivers a powder formulation of olanzapine to the vascular-rich upper nasal space (Phase I)
- BXCL501 is an investigational oral thin film formulation of dexmedetomidine, a selective alpha-2 receptor agonist (Phase II)
- Offer rapid, IM-like absorption rates without requiring an injection
BXCL501: Novel Rapid Treatment of Agitation

Phase 3, randomized, placebo-controlled study (n=380)

- Primary endpoint: mean PEC total score was 17.6
- LS mean change from baseline to 120 minutes for the PEC total score was -4.8, -8.5, and -10.3 for placebo, BXCL501 120 mcg, and 180 mcg, respectively (LSM difference -3.7 and -5.5, p<0.0001 vs. placebo)
- No severe or serious AEs were reported in the study
  - Somnolence was reported by 57 (22%) of BXCL501 participants (49 were mild and 8 were moderate severity)
- FDA fast track designation

PEC: PANSS-Excited Component scale

Electroconvulsive Therapy (ECT)

- Neither ECT alone or as adjunct to antipsychotic therapy seems effective for agitation.

Coping After a Violent Event in the Clinical Setting

• Important to debrief afterwards
• Create a safe environment for one another
• Offer support: “stay with one another”
• Listen
Summary

• Patient assault on clinicians is a very serious situation, with long-lasting physical, psychological, and employment consequences.

• These events can be prevented through assessing risk factors that pertain to the organization, the clinician directly, and the work environment.

• The development of a violence prevention program can be very effective at monitoring these risks, and preventing escalating events to violent occurrences.

• Offering support and a safe environment after a violent incident occurs may improve healing and recovery for victims and witnesses of workplace violence.
Summary

• The first-line treatment of agitation is non-pharmacological, involving environmental modifications and de-escalation techniques

• Pharmacological strategies may be necessary to avoid the escalation of agitation into aggressive and violent behaviors

• The atypical antipsychotics are recommended first-line, with several rapid-acting IM formulations available that seem to be at least as efficacious as IM conventional antipsychotics or benzodiazepines

• Inhaled formulations of antipsychotics may offer the rapid onset of action of an IM antipsychotic with the less invasive characteristic of an oral formulation

• Investigational drug products could offer unique, non-invasive, acute agitation management strategies for patients with psychosis or mania
The ideal pharmacological treatment for agitation should be easy to administer in a way that is non-traumatic for the patient, provide rapid tranquilization without excessive sedation, have a fast onset and sufficient duration of action, and a low risk for adverse effects. Which of the following treatment options fulfills all of these requirements?

1. Intramuscular aripiprazole
2. Oral clozapine
3. Inhaled loxapine
4. Intramuscular lorazepam
5. None of the above
Dr. Jacobs has been treating a diabetic patient with a violent history in the state hospital for several weeks. When she tells the patient that they cannot have a donut, the patient becomes increasingly agitated and shouts, “I’m going to beat you to a pulp!” at Dr. Jacobs.

What should Dr. Jacobs do to prevent the patient from escalating to violent behavior?

1. Listen and empathize with the patient
2. Be on her feet and ready to take action/escape
3. Tell another member of the team/superior what happened
4. 1 and 2
5. All of the above
Appendix
Assessment Tools

• Agitation Severity Scale (ASS)
• Behavioural Activity Rating Scale (BARS)
• Brief Agitation Measure (BAM)
• Clinical Global Impression Scale for Aggression (CGI-A)
• Cohen-Mansfield Agitation Inventory (CMAI)
• Overt Aggression Scale (OAS)
• Overt Agitation Severity Scale (OASS)
• Positive and Negative Syndrome Scale Excited Component (PANSS-EC)
• Staff Observation Aggression Scale (SOAS)
• Broset Violence Checklist (BVC)
• The Historical, Clinical, Risk Management-20 (HCR-20)
• The McNiel-Binder Violence Screening Checklist (VSC)

Workplace Violence Program Checklists

- Checklists can help you and your workplace prevent violence from occurring
- Adapt each checklist to fit your own needs
- These are very comprehensive lists and not every question will apply to your workplace
- Cal/OSHA and NIOSH have identified the following risk factors that may contribute to violence in the workplace
- Example workplace checklist

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>YES</th>
<th>NO</th>
<th>Notes/Follow-up Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do employees have contact with the public?</td>
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<tr>
<td>Do they exchange money with the public?</td>
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<td>Do they work alone?</td>
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<td>Do they work late at night or during early morning hours?</td>
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<td>Is the workplace often understaffed?</td>
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<td>Is the workplace located in an area with a high crime rate?</td>
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<tr>
<td>Do employees enter areas with a high crime rate?</td>
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<td>Do they have a mobile workplace (patrol vehicle, work van, etc.)?</td>
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<td>Do they deliver passengers or goods?</td>
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<td>Do employees perform jobs that might put them in conflict with others?</td>
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<tr>
<td>Do they ever perform duties that could upset people (deny benefits, confiscate property, terminate child custody, etc.)?</td>
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<tr>
<td>Do they deal with people known or suspected of having a history of violence?</td>
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<tr>
<td>Do any employees or supervisors have a history of assault, verbal abuse, harassment, or other threatening behavior?</td>
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<tr>
<td>Other risk factors – please describe:</td>
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</tbody>
</table>
## Workplace Checklists: More Examples

<table>
<thead>
<tr>
<th>Does the workplace have:</th>
<th>In Place</th>
<th>Should Add</th>
<th>Doesn’t Apply</th>
<th>NOTES/FOLLOW-UP ACTION</th>
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</thead>
<tbody>
<tr>
<td>Physical barriers (plexiglass partitions, bullet-resistant customer window, etc.)?</td>
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<tr>
<td>Security cameras or closed-circuit TV in high-risk areas?</td>
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<td>Panic buttons?</td>
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<tr>
<td>Alarm systems?</td>
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<tr>
<td>Metal detectors?</td>
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<tr>
<td>Security screening device?</td>
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<tr>
<td>Door locks?</td>
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<tr>
<td>Internal telephone system to contact emergency assistance?</td>
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<td>Telephones with an outside line programmed for 911?</td>
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<td>Two-way radios, pagers, or cellular telephones?</td>
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<td>Security mirrors (e.g., convex mirrors)?</td>
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<tr>
<td>Secured entry (e.g., “buzzer”)?</td>
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<td>Personal alarm devices?</td>
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<td>“Drop safes” to limit the amount of cash on hand?</td>
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<tr>
<td>Broken windows repaired promptly?</td>
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<tr>
<td>Security systems, locks, etc. tested on a regular basis and repaired promptly when necessary?</td>
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<table>
<thead>
<tr>
<th>All Areas</th>
<th>Some Areas</th>
<th>Few Areas</th>
<th>No Areas</th>
<th>NOTES/FOLLOW-UP ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are patients or clients in waiting areas clearly informed how to use the department’s services so they will not become frustrated?</td>
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<tr>
<td>Are waiting times for patient or client services kept short to prevent frustration?</td>
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<td>Are private, locked restrooms available for employees?</td>
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<tr>
<td>Is there a secure place for workers to store personal belongings?</td>
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