



Therapeutic Challenges Following Antipsychotic-induced Angioedema: A Case Report and Review of Literature



Nona Nichols, MD¹; Jonathan Punzi, MD²; Madison Plasket, RN²; & Morgan Faeder, MD, PhD²
¹Cleveland Clinic, Cleveland, OH; ²University of Pittsburgh Medical Center, Pittsburgh, PA

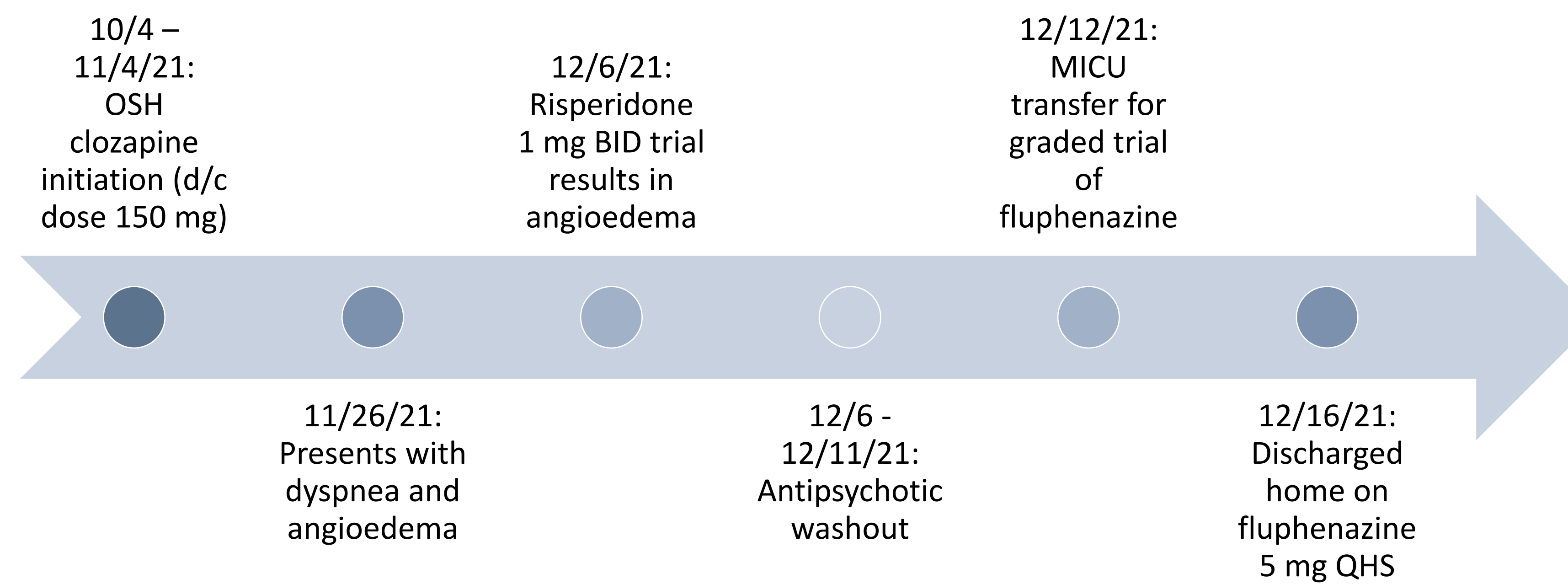
BACKGROUND

Angioedema is a serious inflammatory drug reaction involving subcutaneous or submucosal swelling, which can be deadly when the tongue or upper airways are involved.¹ Multiple case reports have shown an association of angioedema with multiple antipsychotics including chlorpromazine, clozapine, haloperidol, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.² Unfortunately, cross-reactivity within antipsychotic classes is a concern when determining subsequent treatments in patients with ongoing psychosis, though there is limited literature regarding this.²⁻⁴ Here, we present the case of a patient with angioedema initially attributed to clozapine which was recurrent with risperidone whom we successfully treated with fluphenazine.

CASE

- Ms. R, a 55 yo with hypothyroidism, HTN, schizoaffective disorder, and pseudocyesis presented with dyspnea of several hours' duration. She was found to have angioedema, requiring fiberoptic intubation (**Figure 1**), which was initially attributed to carvedilol given prior allergy to antihypertensive medication.
- Psychiatry consulted due to concern that clozapine had caused swelling; it was added during a recent hospitalization. During the same hospitalization, patient also had an episode of angioedema ultimately attributed to lisinopril.
- After discussion with care teams, risperidone 1mg BID (previously tolerated) was started given ongoing psychosis.
- Patient again developed angioedema requiring epinephrine and dexamethasone.
- Washout period instated with plans for loxapine initiation in controlled environment (ICU) after 5-7 period given prior report of success in a cross-tolerance SGA case.²
- Patient later reported she had not been taking clozapine at home and had restarted prior risperidone because she was concerned clozapine would harm her pregnancy.

Figure 1: Timeline of Antipsychotic Administration and Angioedema



CASE, CONT.

- Decision made not to restart clozapine due to ongoing pseudocyesis and likelihood that patient would self-discontinue.
- After a 6-day washout, patient trialed on fluphenazine 2.5 mg, which was chosen because it could be diluted for graded challenge in ICU. Pharmacy was unable to dilute loxapine.
- As there were no adverse reactions, dosing increased to BID and was consolidated to 5 mg QHS at time of discharge 4 days later.
- She continues to do well, without recurrence of angioedema.

Figure 2: Prior Literature Regarding Angioedema Cross-Reactions

| | |
|---|--|
| Cross-reactivity between clozapine, olanzapine, and quetiapine² | <ul style="list-style-type: none"> Pt treated on clozapine (dibenzodiazepine class)⁵ for years develops angioedema during re-initiation. Following washout, olanzapine (thienobenzodiazepine class)⁶ started, resulting in angioedema. Similarly, quetiapine (dibenzothiazepine class)⁷ also resulted in facial edema Loxapine (dibenzoxazepine class)⁸ trialed with good results |
| Cross-reactivity between haloperidol and iloperidone³ | <ul style="list-style-type: none"> Pt develops angioedema after initial haloperidol (phenylbutylpiperadine class)⁹ dose Similarly developed angioedema during iloperidone (piperadine class)¹⁰ titration |
| Cross-reactivity between clozapine and olanzapine⁴ | <ul style="list-style-type: none"> Pt stable on clozapine for 5 years develops angioedema Following washout period, olanzapine was trialed with recurrent angioedema Quetiapine trialed with good results |

DISCUSSION

- ❖ **Consider antipsychotics as a cause of angioedema.** Patient's initial angioedema could have been due to clozapine rather than antihypertensive medication
- ❖ **While angioedema usually occurs within the first week of initiating new therapy, attacks can occur weeks or months after initiating a new medication.**¹ Ms. R had multiple prior successful trials with risperidone in the past without issue.
- ❖ **Prior literature indicates intuitive cross-reactivities among classes of antipsychotics are not consistently reliable when it comes to angioedema (Figure 2).**²⁻⁴ Clozapine, risperidone, and fluphenazine are in three separate derivative classes (dibenzodiazepine,⁵ benzisoxazole,¹¹ and phenothiazine,¹² respectively). Loxapine and clozapine are structurally similar, yet patients who have not tolerated clozapine and medications structurally dissimilar to clozapine have tolerated loxapine.²
- ❖ **Careful liaising between allergy and psychiatry was essential for this outcome,** and multiple discussions were held between teams to determine best and safest course for patient in terms of mental and physical health.
- ❖ **Consider use of fluphenazine in patients who have developed angioedema on other antipsychotic medications.**

REFERENCES

- Salih, I. and Thomas, S. (2006). Causes and management of drug-induced angioedema. *Prescriber*, 17: 14-18.
- Williams G. D. (2019). Cross-reaction of angioedema with clozapine, olanzapine, and quetiapine: A case report. *The mental health clinician*, 9(5), 315-317.
- Muzyk, A. J., Cvelich, R. G., Kincaid, B. R., & Preud'homme, X. A. (2012). Angioedema occurring in patient prescribed iloperidone and haloperidol: a cross-sensitivity reaction to antipsychotics from different chemical classes. *The Journal of neuropsychiatry and clinical neurosciences*, 24(2), E40-E41.
- Tatar, Z. B., Oflaz, S., & Baran, B. (2014). A case of late-onset angioedema associated with clozapine and redevelopment of angioedema with olanzapine. *Journal of clinical psychopharmacology*, 34(4), 523-525.
- National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 135398737, Clozapine.
- National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 135398745, Olanzapine.
- National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 5002, Quetiapine.
- National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 3964, Loxapine.
- National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 3559, Haloperidol.
- National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 71360, Iloperidone.
- National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 5073, Risperidone.
- National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 3372, Fluphenazine