ABSTRACT & COMMENTARY

OnabotulinumtoxinA and the Bladder

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Dr. Ghetti reports no financial relationships relevant to this field of study.

SYNOPSIS: Intradetrusor onabotulinumtoxinA may be a second-line treatment option for overactive bladder in appropriate patients. Health care providers should thoroughly counsel patients on risks and adverse events associated with onabotulinumtoxinA toxin injections.


T his joint Committee Opinion of the American College of Obstetricians and Gynecologists and the American Urogynecologic Society discusses the use of onabotulinumtoxinA for the treatment of overactive bladder (OAB). The FDA approved onabotulinumtoxinA for cystoscopic injection in the detrusor muscle for the treatment of neurogenic bladder in 2011 and for the treatment of OAB in January 2013. The use of botulinum toxin in the bladder has been associated with a significant improvement in OAB symptoms. Intradetrusor onabotulinumtoxinA injections may be a second-line treatment option for OAB in appropriate patients after comprehensive counseling. Shared decision-making between patient and provider should include discussion of contraindications, risks, benefits, and post-procedural adverse events, which include the risk of post-procedure urinary retention, urinary tract infections, hematuria, pain, and transient body weakness. Providers who perform onabotulinumtoxinA injections must have appropriate training and experience in treating women with pelvic floor disorders, operative cystoscopy privileges, and the ability to diagnose and manage any adverse outcomes after onabotulinumtoxinA injections into the bladder.

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The International Continence Society has defined OAB as a bladder syndrome that includes, "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology."1 Urinary urgency is the sudden and compelling desire to pass urine, which is difficult to defer, while urinary frequency is the perception...
of having to void too many times during the day. Nocturia is defined as having to wake up once or more per night to void. The prevalence of OAB in women is estimated to be as high as 30%, and the prevalence of OAB increases with age in men and women. OAB has a significant impact on women’s quality of life. Many women experience embarrassment, social isolation, decrease in physical activity and sexual intimacy, as well as decreased productivity. OAB has been associated with depressive symptoms and is an independent risk factor for falls since nocturia is common. OAB also has a large societal impact, and in 2009, it was estimated that more than $24.9 billion was spent on OAB.

The American Urologic Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogynecology (SUFU) approved guidelines for the diagnosis and treatment of OAB in 2012. The treatment options are divided in first-, second-, and third-line treatments. First-line therapy for all patients with OAB should include education about lower urinary tract function and behavioral therapies that include fluid management, bladder training, and pelvic floor muscle training. These behavioral therapies may be combined with antimuscarinic therapies, which are considered second-line treatments and include, in alphabetical order, darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium. A different antimuscarinic can be used if patients experience inadequate symptom relief or unacceptable side effects. Antimuscarinics are contraindicated in patients with narrow angle glaucoma and should be used with caution in elderly or frail patients, patients with delayed gastric emptying or urinary retention, or patients already using other anticholinergic medications. The medical management of OAB may need to undergo some modifications as we gain more information about the long-term effects of anticholinergic use. In a recent article published in *JAMA Internal Medicine*, the authors report that higher cumulative anticholinergic use is associated with an increased risk for dementia based on a prospective population-based cohort study.

Third-line treatment for OAB includes sacral neuromodulation. OnabotulinumtoxinA, a second-line treatment, has been FDA approved since the publication of the AUA/SUFU guidelines. The randomized, controlled trial reported by Visco et al supports the use of onabotulinumtoxinA as a second-line treatment. In this double-blind, double-placebo-controlled, randomized trial involving women with idiopathic urgency urinary incontinence, patients were assigned to either daily oral anticholinergic medication plus one intradetrusor injection of saline or one intradetrusor injection of 100 U of onabotulinumtoxinA plus daily oral placebo. In the 247 women treated, similar reductions in daily episodes of urgency incontinence were seen in subjects treated with oral anticholinergic therapy and those treated with onabotulinumtoxinA by injection. The group treated with onabotulinumtoxinA was less likely to have dry mouth side effects and more likely to have complete resolution of urgency urinary incontinence than the group treated with anticholinergic medications. However, the group treated with onabotulinumtoxinA had higher rates of transient urinary retention and urinary tract infections.

Botulinum toxin is a powerful neurotoxin derived from the anaerobic bacterium *Clostridium botulinum*. There are seven types of toxin, labeled A-G. Botulinum toxin acts as a muscle paralytic by inhibiting the release of acetylcholine from presynaptic vesicles from motor neurons at the neuromuscular junction. The literature regarding the use of botulinum toxin onabotulinumtoxinA for overactive bladder has been reviewed in a Cochrane review. There is clear level I evidence to support the use of botulinum toxin as an effective and safe therapy in women with neurogenic and idiopathic urge incontinence.

Use of onabotulinumtoxinA is contraindicated in patients with known hypersensitivity to onabotulinumtoxinA, dysphagia, preexisting neuromuscular disorders (myasthenia gravis), and compromised respiratory status. There are no adequate and well-controlled studies in pregnant women, and it is considered an FDA Pregnancy Category C drug.

Candidates for onabotulinumtoxinA should be counseled about its risks and the possibility of post-procedure adverse events, including urinary retention, urinary tract infection, hematuria, and weakness. Patients should have close post-procedure follow-up to assess the effectiveness of the injection and an in-office evaluation of bladder emptying. Only clinicians who are trained in treating women with pelvic floor disorders, who have operative cystoscopy privileges, and who have the ability to diagnose and manage any post-procedure adverse events should perform onabotulinumtoxinA injections. Many subspecialists in female pelvic medicine and reconstructive surgery and urologists are qualified to inject onabotulinumtoxinA for OAB.
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Using Etonogestrel Implants and LNG-IUDs Past FDA-approved Duration

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a consultant for Actavis and Bayer and receives grant/research support from Bayer.

SYNOPSIS: In this small prospective cohort study, use of the etonogestrel implant and the levonorgestrel intrauterine device for an additional year past their FDA-approved duration was associated with an acceptably low failure rate.


This is a prospective cohort study of 237 etonogestrel implant users and 263 52 mg levonorgestrel intrauterine device (LNG-IUD) users who were enrolled between January 2012 and November 2014. The participants were recruited through advertising (12%) and also through previous participation in the Contraceptive CHOICE project (88%) in the St. Louis, MO, area. Women were eligible if they were English- or Spanish-speaking, aged 18 to 45 years, sexually active with a male partner, wanted to avoid pregnancy for at least 12 months, and were within 3 months of or beyond the current FDA-approved duration of use of their device. Method expiration date was validated in 91.8% of the sample through medical records. After initial enrolment, participants were followed with telephone surveys every 6 months and, for those with the implant, etonogestrel assays annually, at the time of method removal, or if pregnancy occurred.

For this analysis, 123 of the 237 implant users had the implant for an additional year and 34 for an additional 2 years. Among these users, there have been zero pregnancies for a failure rate of 0 (one-sided 97.5% confidence interval [CI], 0.1-1.61). The median etonogestrel level at 3 years of use was 188.8 pg/mL (range 63.8-802.6 pg/mL) and at 4 years of use, 177.0 pg/mL (range 67.9-470.5 pg/mL). There were no differences in etonogestrel levels at year 3 or 4 by body mass index class (29% normal weight, 25% overweight, 46% obese). Of the 263 LNG-IUD users, 108 had the device for an additional year. One pregnancy has been documented in the LNG-IUD group for a failure rate of 0 (one-sided 97.5% confidence interval 0-1.61). The median etonogestrel level at 3 years of use was 188.8 pg/mL (range 63.8-802.6 pg/mL) and at 4 years, 177.0 pg/mL (range 67.9-470.5 pg/mL). Nevertheless, the authors of this study report that the etonogestrel implant maintained its effectiveness up to 4 years, even in women who were overweight or obese. Traditionally, a level of 90 pg/mL of etonogestrel has been judged sufficient to suppress ovulation. The median etonogestrel level at 4 years among the 47 women who underwent venipuncture was well above this threshold. Even if the level drops below 90 pg/mL, the authors speculated that other mechanisms of action may provide contraception besides ovulation suppression such as thickening cervical mucus. As they continue to recruit and follow participants, they will be able to assess the relationship between etonogestrel level and contraceptive efficacy by clinical outcome (unintended pregnancy).

Levonorgestrel levels were not measured in IUD users, as the mechanism of action for the device is locally on the uterus and cervix. A previous systematic review of extending

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LNG-IUD use beyond 5 years concluded that based on previous studies, extending the device to 7 years was safe and effective. However, this review was criticized, as two of the four studies cited used 60 mg LNG-IUDs. Since the rate-controlling membrane is proprietary, it is unknown if this device would function like the currently marketed 52 mg LNG-IUD product. In addition, the two other studies cited were small prospective studies of 109 and 67 women, respectively. In a timely fashion, this current analysis answers the call for more prospective data with the currently marketed U.S. product.

This report is definitely reassuring, although I doubt the manufacturers will want to apply to the FDA to change their labeling, as that would not make business sense. Therefore, we cannot rely on the FDA to inform us when and if we can counsel our patients about extended use. Personally, I would like to see more data, especially in younger women before I recommend routinely extending use. I don’t think patients can be told that the LNG-IUS is good for 7 years at this point (although some providers are doing just that), especially if failure would be devastating to the patient. The only population that I may use this information in would be perimenopausal women who have a low likelihood of pregnancy. Either way, certainly documenting a discussion with the patient about the limitations of the current evidence and the off-label nature of the recommendation is necessary. Hopefully, we will have more data in the future from these investigators to allow us to confidently extend the duration of use.

REFERENCES

ABSTRACT & COMMENTARY

Intrauterine Insemination Outcomes Are Not Affected by Sperm Morphology Parameters

By Michael A. Thomas, MD

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Dr. Thomas reports no financial relationships relevant to this field of study.

SYNOPSIS: Pregnancy rates following intrauterine insemination are not affected by abnormalities of sperm morphology.


Semen analysis (SA) is the primary method of evaluating the fertility potential of the male partner. Parameters include sperm concentration (count x 10^6/mL), motility (percent that are moving), and morphology (percent demonstrating normal appearing head, midpiece, and tail). This retrospective chart review evaluated whether isolated abnormal sperm morphology (SSM) in men with otherwise normal concentration and motility affected pregnancy rates when utilizing intrauterine insemination (IUI). A total of 408 couples undergoing 856 IUI cycles were observed. Use of a sperm donor was an exclusion for entry into the study. Couples with isolated abnormal SSM (≤ 4%, n = 352) were compared to those with normal SSM (> 4%, n = 504). Between the two groups, men with abnormal SSM (mean 2.4% ± 1.2) were of lower age, more likely to have undergone a urologic evaluation, more often diagnosed with male factor infertility (oligospermia, varicocele), and had fewer concurrent female infertility problems. Those with normal SSM had a higher incidence of prior pregnancies, lower rates of unexplained infertility, and lower rates of female factor infertility diagnoses (endometriosis, tubal disorders, and uterine factors). No differences were noted between the two groups with respect to a diagnosis of diminished ovarian reserve, anovulation, female obesity, male hypogonadism, or previous azoospermia. Pregnancy rates (defined as an ongoing pregnancy with fetal heart tones) were not different between couples with abnormal (17.3%) or normal (16.7%) SSM (odds ratio, 0.954; 95% confidence interval, 0.66-1.37). There was no significant difference in pregnancy rates when stratified by morphology: 0-2% (16.7%, 126 cycles), 3-4% (17.2%, 180 cycles), 5-6% (16.4%, 126 cycles), and 7-10% (14.2%, 183 cycles). However, compared to men with normal SSM, male partners with low SSM had lower pregnancy rates if they had a palpable varicocele, but higher rates if they had ejaculatory dysfunction. Concurrent female factors did not have an effect on men in either observation group.

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Infertility affects one out of six couples, with male factor present in 30-50% of these individuals and the sole cause in 20%. In the 1950s, the World Health Organization (WHO) adopted the parameters for normal SA based on data from 1000 fertile and 1000 subfertile men. These
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Diagnostic Concordance in Breast Biopsies

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SYNOPSIS: A comparison of breast biopsy diagnosis by clinical pathologists found a 75% concordance with a consensus-derived expert diagnostic interpretation. Concordance was lowest with the diagnosis of atypical, with under-diagnosis noted in 35% of cases.
Management and research outcomes for patients with breast cancer are determined by the pathologic evaluation of a breast biopsy as benign, atypical, ductal carcinoma in situ (DCIS), or invasive. To determine whether U.S. clinical pathologists generally agree on the diagnosis of a clinical case, the authors invited pathologists from eight states to review and classify a series of breast cancer cases. Responding pathologists were asked about their experience with breast cancer diagnosis, and received feedback on their performance and CME credit for participation. The slide sets were developed by a group of three pathologists who arrived at a diagnosis in each case through a consensus process. A total of 240 consensus-derived reference breast biopsy cases (23 invasive breast cancer, 73 DCIS, 72 atypical hyperplasia [atypia], and 72 benign cases without atypia) were available. Each slide set contained a similar distribution of the four consensus-based diagnoses. A greater proportion of each set were atypia and DCIS, as it was expected that these diagnoses would have the greatest degree of discordance. Each participating pathologist reviewed one of four subsets of these cases consisting of 60 slides and was asked to interpret each case as they would in their own clinical practice.

Overall, 65% of the invited, responding pathologists were eligible and consented to participate, and 91% (n = 115) completed the study. The overall concordance rate of diagnostic interpretations of participating pathologists compared with the consensus-derived reference diagnosis was 75% (95% confidence interval, 73.4%-77.0%). Consensus was highest for the diagnoses of invasive breast cancer (96%) and benign without atypia (87%). For benign cases, 13% of cases received an over-interpretation, and 4% of cases of invasive cancer received an under-interpretation. For DCIS, concordance was 84%; 3% of cases with over-interpretation and 13% under-interpretation. The rate of concordance was lowest for atypia (48%); 17% of cases with over-interpretation and 35% under-interpretation. In a regression analysis, pathologists from outside of academic settings, those who interpret lower weekly volumes of breast cases, and those from small-sized practices were statistically significantly less likely to agree with the consensus-derived reference diagnosis.

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The fact that pathologists can’t agree on a diagnosis is not new, and the problem is not restricted to their field. Nevertheless, this paper got plenty of attention on the television news, blogs, and print media. Nothing scares women more than breast cancer, so any story that increases anxiety and raises controversy sells papers and is sure to bring in phone calls to the office.

So let’s dissect the paper. First, the finding that pathologists don’t always agree on a diagnosis is not novel to breast cancer. Lack of agreement has been reported previously for breast cancer, colon cancer, and other diseases. While we all believe that our practice of medicine is evidence-based, we also recognize that diagnosis is an art. In every specialty, there are the few textbook cases, and then everything else. Expertise develops through exposure to lots of mistakes either personal or, hopefully, through education and feedback. Clinicians practicing at academic centers exposed to residents, students, clinical grand rounds, educational seminars, and regular peer review have more exposure to mistakes made by others and the guidance of senior colleagues. Experienced and engaged senior partners in community practice also provide a vital link to the art. Continuing variation is a hallmark of biology, so it is not surprising that we need to see more than 50 shades of grey.

Next, this paper is not a condemnation of community pathologist. When the three reference pathologists performed an initial independent evaluation of the reference cases, they agreed unanimously on the diagnosis for only 75% (180 of 240). Although the eventual overall concordance of these initial independent diagnoses with the consensus diagnosis was 90.3%, it is important to keep in mind that these pathologists were an experienced group of experts with access to the entire set of slides for each case.

The good news is that the concordance agreement for the study group of pathologists was high for invasive cancer (96%) and for benign (87%) biopsies. In other words, over-interpretation of benign without atypia breast biopsies (13%) was more common than under-interpretation of invasive breast cancer (4%). However, the news reports centered on the diagnosis of atypia (17% of cases with over-interpretation and 35% under-interpretation) and DCIS (3% of cases with over-interpretation and 13% under-interpretation). The simple bottom-line recommendation would be to get another opinion with biopsies of undetermined significance and to obtain this opinion from a pathologist at a high-volume cancer center.

The question of whether women are harmed by over- or under-interpretation is less clear. When a biopsy is over-interpreted a woman may undergo unnecessary surgery, radiation, or hormonal therapy. She might also feel pressure to initiate or continue heightened surveillance. Even without surgery or medical treatment, this is stressful and costly. But, what about under-diagnosis? Since many women with DCIS may opt for aggressive surgical treatment, the upgrade of a diagnosis of atypia could have profound implications. Were there a clear benefit of early diagnosis and treatment of DCIS, this would be important. However, the natural history of DCIS is not clear, and we still cannot reliably predict which women are at risk for progression. Mastectomy for DCIS confers no survival advantage and may represent overtreatment for most patients with DCIS. So maybe the under-diagnosis of atypia rather than DCIS is actually protective for some women?

In the future, a better understanding and use of molecular profiling will ensure that surgery and adjuvant treatments are restricted to those patients at highest risk of serious breast cancer and invasive recurrence. All the more reason...
to make sure your patient with atypia or DCIS receives a full consultation from specialists who are up to date and capable of providing detailed counseling about all of the latest medical and surgical options, including the option for no treatment and active follow-up for low risk women.\textsuperscript{4}

**SPECIAL FEATURE**

**Low-lying Intrauterine Devices: To Remove or Not to Remove?**

*By Rebecca H. Allen, MD, MPH*

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Dr. Allen reports she is a consultant for Actavis and Bayer and receives grant/research support from Bayer.

It is not uncommon that we receive reports from radiology regarding the location of an intrauterine device (IUD) in a patient that we have sent for a pelvic ultrasound examination for an entirely different reason (e.g., an adnexal mass). These incidental findings of low-lying or malpositioned IUDs are a conundrum for the practitioner. Many questions arise when attempting to counsel the patient:

- Will the IUD be effective for contraception?
- Will the IUD be effective for abnormal uterine bleeding if it is the 52 mg levonorgestrel IUD?
- Is the IUD responsible for any symptoms due to its position, such as abnormal uterine bleeding or pelvic cramping?
- Does it matter if it is in the lower uterine segment or cervix?
- Should the IUD be removed and replaced?

If you are not sure what to do about low-lying IUDs, you are not alone. A survey of providers in the United Kingdom and Australia revealed that there is some level of uncertainty about what to do.\textsuperscript{1} Approximately 90\% of providers stated they would remove and replace a copper IUD that was totally or partially in the cervical canal, but only 45\% would replace a copper IUD that was more than 2 cm below the fundus and only 10\% if it was 1 to 2 cm below the fundus. The numbers were similar for levonorgestrel IUDs. Respondents also had divided opinions as to whether low-lying IUDs cause bleeding and pain symptoms more often than normally situated IUDs.

Whether malpositioned IUDs have decreased contraceptive efficacy is unclear. Studies concluding that low-lying IUDs are associated with contraceptive failure typically examine cases of pregnant women with an IUD in situ compared to non-pregnant women. One study reported that IUDs were displaced into the cervix in 13/25 (52\%) pregnant women and 7/97 (7\%) non-pregnant women.\textsuperscript{2} However, it is unknown if the growing pregnancy pushed the IUD into a low-lying position. In other words, which came first, the low-lying IUD or the pregnancy? Studies examining risk factors for IUD failure are few and none have examined IUD location in relation to failure prior to pregnancy being diagnosed.\textsuperscript{3} The best evidence evaluating IUD location and failure involves only the levonorgestrel IUD. In a randomized, controlled trial, 151 women had a 20 mcg/day-releasing levonorgestrel IUD placed intracervically and 147 at the uterine fundus.\textsuperscript{4} There were no differences between the two groups after 5 years of follow-up in terms of pregnancy rates. This seems to indicate that the levonorgestrel IUD is effective no matter where it is placed in the uterine cavity. This makes sense given that the main mechanism of action is thickening cervical mucus. However, no such data are available for the copper IUD.

Assuming an incidentally found malpositioned IUD in an asymptomatic patient, the risks and benefits of removal must also take into account the subsequent contraceptive option chosen by the patient. One retrospective study of 182 women with malpositioned IUDs (73\% in the lower uterine segment or cervix, 11.5\% embedded and/or rotated, 7\% expelled, 7\% intraperitoneal, and 19\% with more than one type of malpositioning) found that 121 women had their IUDs removed. Of these women, only 37\% received another long-acting reversible contraceptive or sterilization.\textsuperscript{5} The remaining relied on less-effective methods. Because studies have shown that the IUD can migrate up and down in the uterine cavity with the menstrual cycle, it may be that the device left in place would resume its proper position at a later point.\textsuperscript{6,7} Therefore, removing the device in an asymptomatic patient may be premature.

If the patient has symptoms such as pain and/or bleeding and a malpositioned IUD, providers have debated whether the IUD is responsible for the symptoms. One case-control study evaluated 236 women with an IUD and symptoms of pain and/or bleeding compared to 245 asymptomatic women with an IUD. They found no relationship between IUD location in the cavity based on ultrasound measurements (IUD-endometrium, IUD-myometrium, and IUD-fundus) and symptoms.\textsuperscript{8} In contrast, a study published by Benaceraff et al on three-dimensional ultrasound and IUD location among 167 women found that 21/28 (75\%) women with malpositioned IUDs complained of pain and/
or bleeding compared to 38/139 (34%) women with normal located IUDs. Certainly as a practical matter, clinicians must individualize their treatment of patients and, if other causes of pain and/or bleeding have been ruled out, it is prudent to remove the IUD to see if the symptoms improve. This may hold true to a greater extent for rotated and embedded IUDs compared to IUDs in the lower uterine segment.

A review of the literature on this topic summarized the data into four recommendations:

1. Wait and see if the device moves itself with backup contraception, and review using ultrasound at a later date.
2. Consider attempting to move the device with alligator forceps back up into the cavity, although this depends on operator skill and patient tolerance.
3. Replace the IUD with ultrasound review at 6 weeks. The patient should be advised that the replacement IUD may also become displaced.
4. Remove and choose an alternative contraceptive method.

My own bias for asymptomatic women relying on the device for contraception is to leave low-lying levonorgestrel IUDs in place with appropriate counseling and to remove and replace low-lying copper IUDs. I have not attempted pushing a low-lying IUD back up into the cavity with alligator forceps, although one study demonstrated in a small case series that this was technically possible. Due to the lack of definitive evidence, many of these decisions will involve a frank discussion with the patient regarding the clinical unknowns and their personal preferences.

REFERENCES

CME QUESTIONS

1. In the management of overactive bladder, onabotulinumtoxinA injections may be a second-line option only after education about lower urinary tract function, fluid management, bladder training, and pelvic floor muscle training.
   a. True
   b. False

2. The level of etonogestrel necessary for ovulation suppression is thought to be:
   a. 60 pg/mL
   b. 90 pg/mL
   c. 120 pg/mL
   d. 180 pg/mL

3. In the fifth edition of the WHO sperm laboratory manual, what is the lower limit of normal for sperm concentration?
   a. 5 mil/mL
   b. 10 mil/mL
   c. 15 mil/mL
   d. 20 mil/mL
   e. 25 mil/mL

4. What was the diagnostic agreement of clinical pathologists who responded to a request to review a set of breast biopsies with a consensus-derived expert reference diagnosis?
   a. Good (> 80%) for all categories of biopsies
   b. Good for invasive cancer, benign without atypia, and DCIS, but not for atypia
   c. Good for invasive cancer, benign without atypia, and atypia but not DCIS
   d. Good for invasive cancer, DCIS, and atypia, but not for benign without atypia
   e. Good for benign without atypia, atypia, and DCIS, but not for invasive cancer

[IN FUTURE ISSUES]