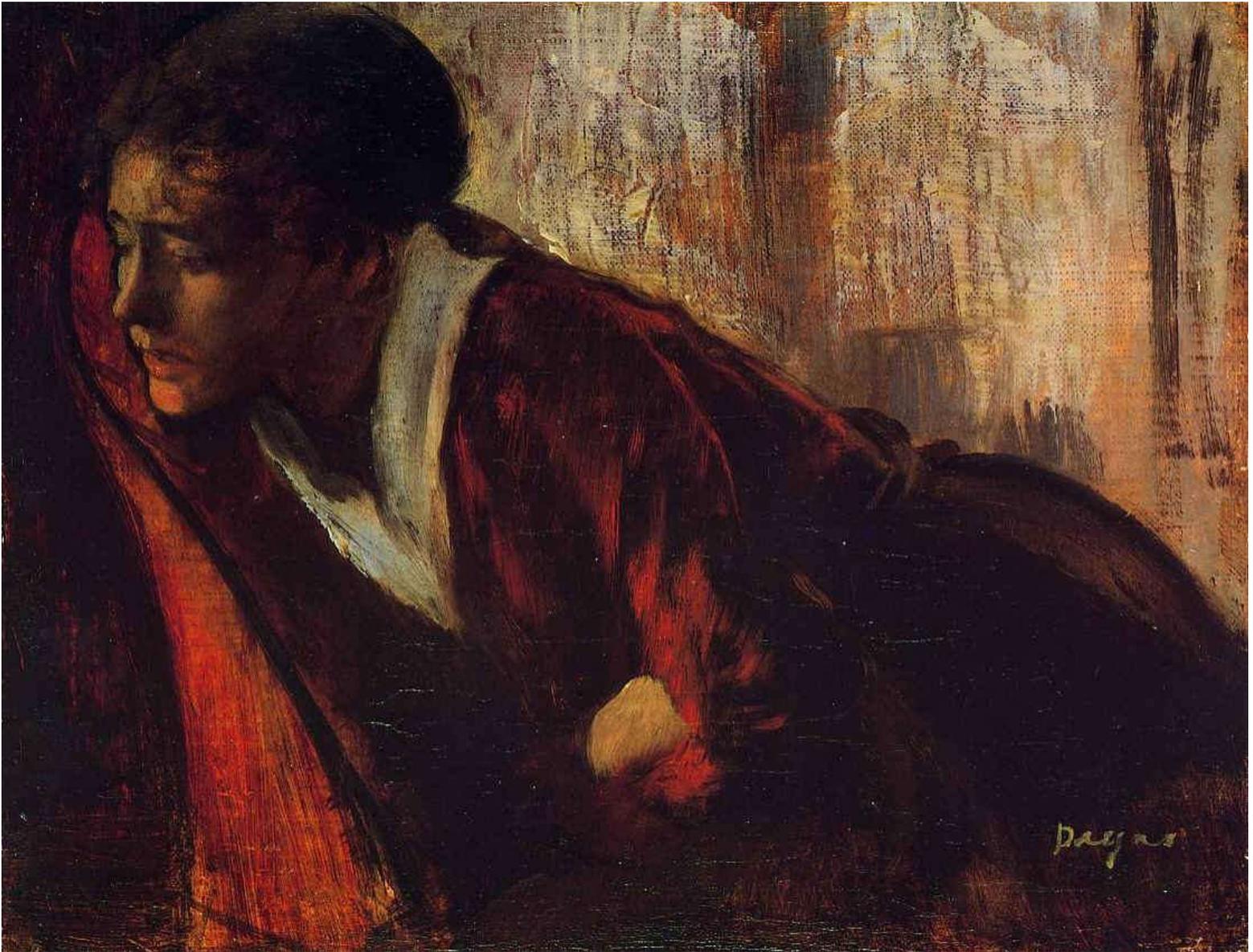


CITALOPRAM



"Melancholy", oil on canvas, 1874, Edgar Degas, Philips Collection, Washington, DC.

What Mary does not tell Edgar....

That sometimes she cannot sell at night because she dreams of texture and shadow, of prints and plates, of ink and burin, of perspective and foreshortening, of light shimmering and colours colliding, of juxtaposition and contrast, of press and pressure, of mordant and hydrochloric acid, and damp and dry paper, of depth of line and shallow, tiny scratches, of third, fourth, and fifth states, of the craft of dimension, of detail and restraint, of the uncommon, the difficult, the true, the sublime. That not enough time exists to accomplish mastery, though she wants it, she dreams of it, she aches for it.

That some days she rues the tyranny of the clock, a devil that instead of recording hours steals them from her, impeding her progress, handicapping her, because she needs time, she is not quick, she is not cavalier, she is not prolific: she is studied, careful, deliberate, cautious even, though no one would believe her - they think her courageous and adventurous, and while it is possible that this is true, they do not know with what reflection she approaches her art even as she strives to be free. That she is hampered by her fear of being irrelevant even as she is determined to not to be. That her father's doubt nags at her, that to have to maintain resistance to skepticism even in her own home exhausts her.

That suddenly the fear that she is not gifted, not skilled, not talented overcomes her and she has to bury the unease so as not to alarm her models and make them question her and in so doing drift away and lose the expression or even the desire to please her and she needs them to want to please her for she does not paint out of doors. She does not paint vases or flowers or rivers, she paints people, she seeks to portray their inner lives, and they will not show them to her if they do not believe she can reveal them. That colour and light is all she has in the world by way of tools.

That though her sharp mind does her well, it can only be deployed through brush and beauty, for she would not be able to run a railway, a bank, a university, though she believes she could if given the chance, though no man would give a woman such leave, but in art all is allowed if one frees oneself of prejudice, which is why she needs the madding rabble of the impressionists in their quarrelsome disagreements, because they never say to her face that she is a woman, though she is one and sometimes, sometimes, she yields and it is this that troubles her, for Edgar is necessary to her and gratitude is not the word to describe her relief that he came to her and rescued her because she had been on the verge of quitting, there were days when she thought "I can't fight them anymore" and surely there was some grand, divine bon mot in the universe that would convey to him what it meant that he had shared his courage, intellect, and artifice with her, that he had befriended her, that he had given her her sight.

That she has had to find a way to say that she needs him without capitulating to the romantic, though as a woman she does sometimes capitulate, for what is more desirable in life than someone who knows you, who finishes your sentences, who challenges you, who gives you what you need, who considers you an equal, who makes your days fuller, brighter, better, and this to her is romantic, it is the heart of romance, a mirrored mind, a matched soul, twinned yearnings, reciprocal intellects, and why this should frighten him she doesn't know, because it does not frighten her, though if he came to her and said "I am yours" what would she say, because Abigail died for love and what other woman has survived marriage intact, childless, free to pursue that which is selfish because art is the thief of time, and love also demands time but then wilts into something other, something institutional, something obligatory, like Berthe's unholy imbalance of motherhood, sisterhood, and marital obligation, a nightmare of subterfuge Mary could never countenance but admires for its honesty because Berthe's desire is for art, it is fully for art, as is hers, but somehow Berthe has managed to love if illicitly and while Mary has painted love and seen love and been admired for seeing and painting love, somehow she has not managed to have love.

That it confounds her that this must be the choice. That she remembers her avowals and declarations and certainties from not so long ago, when she was young and her goals seemed distant and a monastic life necessary to achieve them and she had not hesitated to announce her firm renunciation of the encumbrances of womanhood, but she'd been young then, not yet in love, not yet torn apart by desires so palpable they cause her pain. That it was the pain that surprised her, that it was the love that surprised her, that it was she who was in need of the love that astounded her. That life is ungovernable, even for a disciplined soul like hers, and betrayal its practical joke.

Robin Oliveira, "I Always Loved You", Viking, 2014

The late Twentieth century witnessed are-embrace of biology as the basis of mental illness and an increasing neglect of its other dimensions....Parents and their families learnt to attribute mental illness to faulty brain biochemistry, defects of dopamine or a shortage of serotonin. It was biobabble as deeply misleading and unscientific as the psychobabble it replaced - in reality the major forms of madness remain almost as mysterious as ever - but as marketing copy it was priceless. Meantime the psychiatric profession was seduced and bought off with enormous amounts of research funding. Where once psychiatrists had existed in a twilight zone on the margins of professional respectability (their talk cures and obsessions with childhood sexuality only amplifying the scorn with which most mainstream medics viewed them), now they were the darlings of medical school deans, the millions upon millions of their grants and indirect cost recoveries helping to finance the expansion of the medical - industrial complex that has been so notable a development of the years since the Second World War. Much of that financing has come from a pharmaceutical industry that has grown to maturity over the past three quarters of a century. Big Pharma is an international phenomenon these days. Its marketing muscle reaches across the globe. Its search for profitable new compounds ignores national boundaries, except so far as it often retreats to the global periphery to conduct its researches, where ethical constraints are more easily evaded, and the information gleaned from multi-centered clinical trials more easily kept under company control. And its profits are astounding, far exceeding those of many other segments of the economy. That the bulk of them are earned in the free-for-all that is the United States is one of the primary reasons for the growing global hegemony of American psychiatry.

Andrew Scull, "Madness in Civilization", Princeton, 2015.

Traditional late Twentieth century medical teaching dogma had it that depression was essentially of two types, one was "secondary", or "exogenous" that is it was due to a clear precipitating factor or event, clear enough for all to see. The other was more mysterious, a "primary" or "endogenous" depression without any clear precipitating factor or event at all. Big Pharma funded research stepped in announcing that primary depression was simply a "chemical imbalance" that had occurred in the brain - nothing at all to do with the patient's inner fears, emotional state, black spaces, suppressed yearnings, unfulfilled dreams, self doubts, feelings of worthlessness or hopelessness. The cure was quite simple - elevate the brain bio-amines and all of these negative feelings will go away. Big Pharma was more than happy to show the way!

The human psyche is an unimaginably more complex phenomenon than simply the sum total level of its serotonin concentrations. Dark places of the subconscious mind exist in every Homo Sapiens, no matter what their station in life, places that may not be communicated to any outsider under any circumstance, and often not even to the fully conscious mind of the sufferer of so called “endogenous” depression themselves.

In the Philips Collection, Washington, DC hangs a masterpiece by the great French Impressionist, Edgar Degas. An unidentified woman, alone in her darkened room, the firelight reflecting off her face. She hangs over the back of her chair clutching herself lost in some private torment. The work is entitled “Melancholy” and could there be any better depiction of a soul’s private agony? Her deep anguish is plain for any feeling person to see. Degas had a strong and long professional relationship with the American Impressionist Mary Cassatt, but oceans of ink have been spilt over whether or not their relationship was anything closer than professional. We will never know for certain, neither married, both destroyed all of their correspondence to each other near the ends of their lives. We do not know the reason for the woman’s deep “melancholia”; and it does not appear that she will willingly relate it. Late Twentieth century medical dogma would have suggested a mere “chemical imbalance” - simply raise the level of her serotonin and all her suffering will be gone! However, from the sheer intensity of Degas’ work, one suspects not, her agony is a much darker more complex affair than a mere “chemical imbalance”.

The identity of the woman in Degas’s work is (officially) unknown. What is known however is that it was produced in 1874, the year Mary Cassatt moved to Paris and the year Degas first became aware of her work, which he greatly admired. Mary in turn, had seen Degas’ work in a gallery window. It was an instant revelation to her and would become her life-long professional inspiration. Though the date of their first meeting is often quoted as 1877, the model in “Melancholy” bears a striking resemblance to a later self-portrait Mary made of herself in 1878. Could they have in fact met four years earlier in 1874?

The agent citalopram is just one of the “miracle” SSRIs developed off the back of its multi-billion dollar prototype “Prozac” in the 1980s. Late Twentieth century medical teaching would have it that this agent by the simple mechanism of brain serotonin elevation could have transformed Degas’ anonymous melancholic model into a picture of radiant happiness. But chemical manipulation alone can never fully address the darkest places of a human psyche and today it is appreciated that a far more “holistic” understanding is required.

CITALOPRAM

Introduction

Citalopram (trade name in Australia “Celapram” among others) is a **selective serotonin reuptake inhibitor (SSRI)**.

The SSRIs in general are as effective as the first generation antidepressants for the treatment of depression (TCAs and MAOIs) although not nearly as lethal in overdose as those agents, nonetheless they are not without their own significant side effects.

In particular **Citalopram** (and its (S)-stereoisomer or left-enantiomer, **escitalopram**) are more likely among the SSRIs to cause **dose-dependent QT prolongation**.

These two agents are also the most likely to cause **seizures**.

See also separate documents on:

- **SSRI Overdose (in Toxicology folder)**
- **Serotonin Syndrome (in Toxicology folder)**

History

The SSRIs were developed in order to have safer less toxic antidepressants, than the tricyclic antidepressants or MAOIs that were the front line antidepressants of the 1970s and early 1980s.

Fluoxetine was developed by Klaus Schmiegell and Bryan Molloy of the Eli Lilly Company in 1972 and in 1986 became the first SSRI agent to be introduced into medical practice.

Citalopram was developed by scientists at the pharmaceutical company Lundbeck, also in 1972. It was introduced into clinical practice in 1989 in Denmark.

It was introduced in the US in 1998.

Chemistry

Citalopram has one stereocentre, to which a 4-fluoro phenyl group and an N,N-dimethyl-3-aminopropyl group bind.

As a result of this **chirality**, the molecule exists in (two) enantiomeric forms (mirror images). They are termed S (+) citalopram and R (–) citalopram.

Citalopram is sold as a racemic mixture, consisting of 50% (R) (–) citalopram and 50% (S) (+) citalopram.

Only the (S) (+) enantiomer has the desired antidepressant effect.

Lundbeck markets the (S) (+) enantiomer, the generic name of which is **escitalopram**.

Citalopram is supplied as the hydrobromide whereas escitalopram is supplied as the oxalate salt (hydrooxalate).

In both cases, these salt forms of the amine make these otherwise lipophilic compounds water soluble.

Classification

The selective **serotonin reuptake inhibitors (SSRIs)** currently include:

1. Fluoxetine
2. **Citalopram**
3. Escitalopram
4. Fluvoxamine
5. Paroxetine
6. Sertraline
7. Dapoxetine

The **serotonin *and* noradrenaline reuptake inhibitors (SNRIs)** currently include:

1. Venlafaxine
2. Desvenlafaxine
3. Duloxetine

Preparations

Citalopram hydrobromide as:

Tablets:

- 10 mg
- 20 mg
- 40 mg

Mechanism of Action

The SSRIs selectively inhibit the presynaptic reuptake of serotonin (5-hydroxytryptamine, 5HT).

They do *not* block the reuptake of noradrenaline.

Pharmacodynamics

Clinical trials. Citalopram in the dose range **20 - 80 mg/day** is more effective than placebo in the treatment of depression in the majority of trials, including relapse prevention trials.

In humans, citalopram does not impair cognitive function or psychomotor performance to the same extent as amitriptyline

It has slight sedative properties.

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of serotonin (5-HT) uptake. Tolerance to the inhibition of 5-HT uptake is not induced by long-term treatment with citalopram.

Pharmacokinetics

Absorption:

- Citalopram is administered orally.
Oral bioavailability is around 80%

Distribution

- The apparent volume of distribution is about 12-17 L/kg
- Protein binding is around 80%
- Citalopram can cross the human placenta.
- Citalopram is excreted in human breast milk in small amounts.

Metabolism and excretion:

- Citalopram is metabolised by the CYP2C19 system to a number of less active metabolites including de-methyl-citalopram (DCIT), dide-methyl-citalopram, citalopram-N-oxide

There is also an inactive deaminated propionic acid derivative.

All the active metabolites are also SSRIs, although weaker than the parent compound.

Unchanged citalopram is the predominant compound in plasma.

- Elimination half life is 1.5 days
- About 10-25% of the daily dose is excreted unchanged in the urine

Indications

Indications for citalopram include:

1. Major depression
2. Anxiety disorders:
Including:
 - Panic disorder
 - Obsessive-compulsive disorder (OCD)
3. Bulimia nervosa
4. Premenstrual dysphoric disorder

Contra-indications/precautions

These include:

1. Known hypersensitivity to citalopram or escitalopram or to other SSRIs in general
2. Drug interactions:
 - **Caution with other serotonergic agents:**
 - ♥ Coadministration with other serotonergic drugs (e.g. SNRIs, SSRIs, tramadol or triptans such as Sumatriptan, or MAOIs - selective, reversible or irreversible - within a minimum of 14 days) may result in **serotonin syndrome**.
 - **CYP2C19 inhibitors:**
 - ♥ Citalopram is metabolized by the CYP2C19 system: use lower doses if citalopram is combined with **an inhibitor** of CYP2C19 or there is a **genetic lack** of CYP2C19 activity as citalopram's

concentration may increase and so may increase the risk of arrhythmia.

3. Bipolar disorder: ²

- All antidepressants may provoke a manic episode when used in people with **bipolar disorder**.

Some patients *without* a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.

4. Dose should be decreased in hepatic impairment:

5. QT prolongation:

- **Citalopram** (and its (S)-stereoisomer or left-enantiomer, **escitalopram**) are more likely among the SSRIs to cause **dose-dependent QT prolongation** particularly in overdose.

This is greater in doses > 40 mg daily.

Citalopram should be used with caution in patients with conditions such as congenital long QT syndrome; acquired long QT syndrome (e.g. due to concomitant use of a drug that prolongs the QT).

6. Age related:

- **Children < 18 years:**
 - ♥ **Increased** suicidal thoughts and behaviour can occur **soon after** starting any antidepressant, particularly in young people; monitor patients frequently and carefully **early** in treatment.

This is particularly the case with the SSRIs. SSRI use in fact is related to a **higher** overall risk of suicidal behavior in children and adolescents and so SSRIs are **contraindicated** in these age groups.

- **Elderly:**
 - ♥ Use lower doses as concentration and half-life are increased compared to younger people.

7. Bleeding risk:

- Selective serotonin reuptake inhibitors (SSRIs) may increase the risk of bleeding, especially gastrointestinal bleeding, by blocking the uptake of serotonin into platelets.

However, the absolute risk of this is **low**.

The risk is increased by concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulant drugs and antiplatelet drugs.

Patients with liver cirrhosis or liver failure and patients susceptible to gastrointestinal bleeding (e.g. patients with a history of peptic ulcer disease or oesophageal varices, or who are undergoing surgery) are also at increased risk.

Consider an alternative class of antidepressant or the addition of a gastroprotective drug (e.g. a proton pump inhibitor) in patients at increased risk of bleeding.

If NSAID use must be continued, a less gastrototoxic NSAID is recommended (e.g. ibuprofen, diclofenac).

Pregnancy

Citalopram is a category C drug with respect to pregnancy.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Most studies have shown that citalopram has not been associated with any increased risk of congenital malformations above baseline risk in the general population.

However, neonatal withdrawal symptoms may develop due to prenatal exposure to citalopram, especially in late pregnancy. These symptoms include respiratory distress, hypoglycaemia, irritability, temperature instability, sleep disturbance, tremors, jitteriness, difficulties feeding and diarrhoea which can be attributed to serotonergic hyperstimulation. These self-limiting neonatal antidepressant withdrawal symptoms may require some supportive care. Neonatal care providers should be informed about the use of citalopram as potential adverse effects or withdrawal symptoms may be presented in newborns.

Persistent pulmonary hypertension of the newborn (PPHN) is a rare condition, defined as a failure of the pulmonary vasculature to relax after birth with hypoxemia as a result. PPHN can be the result of various underlying pathological conditions. The evidence concerning the association between PPHN is still insufficient to contraindicate the use of SSRI during pregnancy.

Based on the limited information available, long term behavioural and cognitive outcomes among children exposed to SSRI in utero, have shown no significant difference compared to non-exposed children.

Breast feeding

Small amounts of citalopram are excreted into breast milk and no serious harmful effects have been found in breastfed infants.

If citalopram is the medicine of choice, use the lowest effective daily dose and closely observe the breastfed infant for potential adverse effects such as drowsiness, irritability, poor feeding and restlessness. Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

There is still a lack of information regarding the neuro-developmental outcomes of infants exposed to citalopram via breast milk.

Adverse Effects

These include:

1. Allergic / hypersensitivity reactions.
2. GIT upset:
 - Nausea, diarrhoea
3. CNS effects:
 - Drowsiness/ mild sedation.
 - Serotonergic effects which occur in children > adolescents > adults.

These may include:

- ♥ Anxiety / agitation
 - ♥ Panic attacks
 - ♥ Insomnia
 - ♥ Tremor
4. **Serotonin toxicity :**
 - A more serious serotonin toxicity can develop, particularly when used in combination with other serotonergic agents.

Treatment with either moclobemide or a MAOI (or within 14 days of stopping a MAOI or within 2 days of stopping moclobemide) is contraindicated due to the risk of serotonin toxicity. ²

5. Sexual dysfunction
6. Hyponatraemia:
 - This usually occurs early in treatment, and may be asymptomatic. It is due to SIADH.
7. Prolonged QT interval:
 - **Citalopram** (and its (S)-stereoisomer or left-enantiomer, **escitalopram**) are more likely among the SSRIs to cause **dose-dependent QT prolongation**.
8. Children < 18 years
 - Suicidal ideation may paradoxically be increased

Dosing

Usual adult dosing is:

- 20 mg orally once daily

Gradually increasing after 2 - 4 weeks if necessary to a **maximum of 40 mg** once daily.

Maintenance doses > 20 mg daily are not usually necessary in major depression.
- Reduce dose in:
 - ♥ Elderly
 - ♥ Decreased CYP2C19 activity
 - ♥ Hepatic impairment
Oral 10 mg once daily, gradually increasing after 2 - 4 weeks if necessary to a maximum of 20 mg once daily.

When stopping any SSRI treatment it is advisable to taper over several weeks to avoid withdrawal effects; reduce the daily dose by half no faster than weekly.



*"Self-portrait", watercolour, gouache on wove paper c. 1878,
Mary Cassatt, Metropolitan Museum of Art, NY*

References

1. eTG - July 2017.
2. Citalopram in Australian Medicines Handbook Website, Accessed August 2017.
3. Citalopram in MIMs Website 1 August 2016.
4. Citalopram in RWH Pregnancy & Breastfeeding Guidelines, 25 July 2016

Dr J. Hayes
August 2017.