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Evaluating Muscle Weakness Improvement With Lorcaserin in ICU (EMILI)

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JHM IRB - eForm A – Protocol

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1) Abstract

(Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.)

It was recently discovery that patients recovering from sepsis/critical illness have great difficulty recruiting motor units to generate muscle force. Prior to this discovery, the primary etiology of muscle weakness in these patients was thought to be muscle disease (myopathy) and degeneration of peripheral nerve (neuropathy). However, since motor units are composed of a group of muscle fibers contacted by a single motor neuron arising from the spinal cord, these new findings suggested a problem within the spinal cord as the primary cause of weakness in affected patients. Consistent with these clinical findings in critically ill patients, there is a profound deficit in the excitability of motor neurons in the spinal cord of septic rats. Studies characterizing the impaired excitability in rat motor neurons point to a specific deficit in a slowly inactivating type of sodium current (i.e., the persistent sodium current). This type of sodium current has been well characterized in motor neurons; it is known that activation of a subtype of serotonin receptors (5-HT_{2C}) increases this current. In an attempt to normalize motor neuron firing, in prior research septic rats were treated with lorcaserin (a drug approved by the FDA as Belviq® for weight loss via activation of 5-HT_{2C} receptors) and found that motor neuron excitability was normalized such that muscle force production improved 4-fold. The dramatic improvement in strength in rats raises the possibility that lorcaserin might benefit critically ill patients with muscle weakness after sepsis. In this proposal, we propose the first step in translating findings these findings to patients with intensive care unit (ICU)-acquired weakness. Specifically, we will examine the efficacy and safety of lorcaserin in weak critically ill patients recovering from sepsis. We will assess muscle strength after two escalating doses of lorcaserin in these patients.

2) Objectives

(Include all primary and secondary objectives)

2-1) Evaluate the safety of lorcaserin in intensive care unit (ICU) patients recovering from sepsis.

While lorcaserin is safe for prolonged use for weight loss, it has not been used in ICU patients.

2-2) Compare the effect of lorcaserin vs. placebo on muscle strength in ICU patients recovering from sepsis.

3) Background

(Briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

3-a) Severe Muscle Weakness in Critical Illness is a Frequent, Serious and Costly Health Problem

One of the most devastating complications of critical illness is the poorly-understood, rapid and persistent severe weakness of skeletal muscles. In the United States, more than 750,000 people per year have sepsis with 380,000 requiring an intensive care unit (ICU) stay and mechanical ventilation(1). Studies suggest that from 1/3 to 1/2 of patients who require prolonged mechanical ventilation develop global, persistent weakness(2;3). From these data we estimate that in the U.S., 100,000 to 150,000 patients per year develop profound muscle weakness as a result of sepsis-associated critical illness. Development of weakness has an important economic impact, with a 4-fold increase in average hospital cost per patient(4). In addition, weakness results in important long-term impairments in physical functioning, quality of life and delayed return to work(5-7).

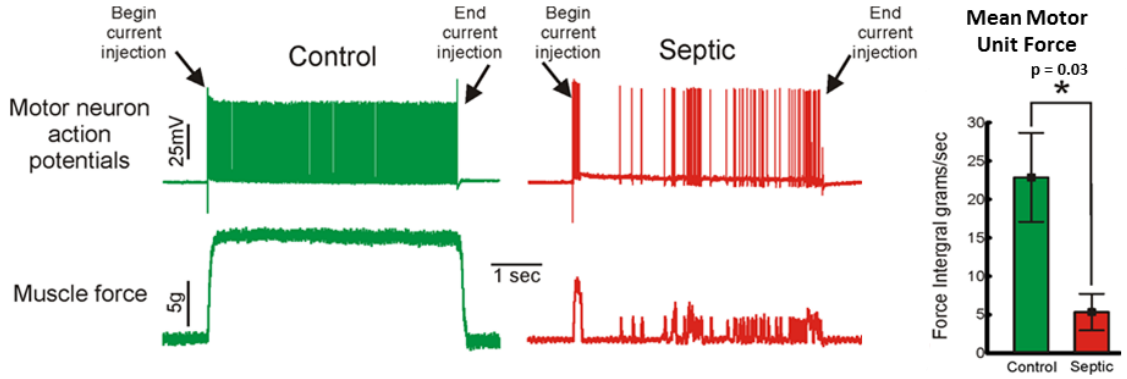
3-b) Incomplete understanding and ineffective treatment

Both a myopathy ("critical illness myopathy" - due to muscle atrophy and loss of myosin), and a neuropathy ("critical illness polyneuropathy" - due to death of axons) contribute to weakness(8;9). However, as reported in a recent study in a rat model(10), neither myopathy nor neuropathy fully account for weakness. A lack of understanding of the mechanisms causing weakness after critical illness has meant that the main therapies available are non-specific interventions, applied in hopes of promoting long-term recovery of neuromuscular function. These therapies include tight glycemic control (11) and physical therapy during critical illness(12;13), but these therapies have sub-optimal effect in patients with severe weakness.

3-c) Our newly published studies identify a novel potential mechanism for central nervous system (CNS) dysfunction in sepsis

A recent prospective study of muscle weakness in ICU patients(14) discovered that a myopathy or neuropathy could not fully explain the virtual paralysis exhibited by some patients who were awake and attempting to produce maximal voluntary contraction. An additional factor became apparent in EMG records of motor unit activity, that demonstrated poor recruitment (both low numbers of motor units recruited and low firing rates) consistently in patients with sepsis-induced weakness(10). Thus, the two primary mechanisms by which the central nervous system regulates muscle force, i.e. recruitment and rate modulation of motor unit firing, were both dramatically reduced. These findings provide a potential novel mechanism to account for CNS dysfunction in septic humans.

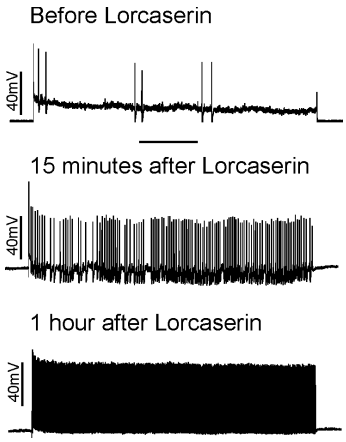
Figure 1- Inability to sustain motor neuron firing causes acute weakness during sepsis in rats



Shown are the motor neuron action potentials and force records from motor units in a control and septic rat during continuous current injection into the motor neuron in the spinal cord *in vivo*. The control motor neuron fires throughout the 5s current injection to generate stable muscle force for 5s. The motor neuron from the septic rat fires erratically, such that muscle force is low and irregular. On the right, the mean values of motor unit force generated in response to a 5s current injection is plotted for 4 control vs. 4 septic rats (p =0.03 for difference in force integral).

Another recently published study demonstrated that, in a rat model of sepsis, there is reduced intrinsic excitability of spinal motor neurons supplying the medial gastrocnemius muscle(10). Excitability of individual motor neurons in the spinal cord *in vivo* was measured in terminal studies of anesthetized adult rats that were either healthy or made septic through the standard cecal ligation and puncture methodology. Statistical comparison of motor neurons sampled from septic and healthy rats revealed a striking and consistent difference in repetitive firing evoked by intracellular current injection. Repetitive firing of individual motor neurons in septic rats was slower and more erratic such that septic motor neurons fired 1/3 as many action potentials during a 5 second current injection(10). None of the previously reported reductions in muscle and nerve excitability described with critical illness are this dramatic and rapid in onset. Shown in Figure 1 are i*n vivo* recordings of the action potentials and single motor unit force generated during 5 second stimulation of a motor neuron from a control rat (green) and a septic rat (red). The septic motor neuron is unable to sustain firing and generates <20% of the force generated by the control motor neuron. On the right side of Figure 1 is a plot of the mean values of motor unit force generated in response to a 5s current injection for 4 control vs. 4 septic rats (p =0.03 for difference in force integral). This reduced motor neuron excitability persists for at least 1 week following cecal ligation and puncture. Hence, these studies raise the possibility that reduced motor neuron excitability may be the most important cause of acute weakness during, and in the early phase of recovery from, sepsis.

Figure 2: Increasing sodium current with lorcaserin normalizes motor neuron excitability in a septic rat.



Shown are three response to a 5s current injection in a single motor neuron from a septic rat before and at two times after injection of 3 mg/kg lorcaserin. Before lorcaserin, the motor neuron fires action potentials only infrequently during the 5s current injection. 15 minutes after lorcaserin, the motor neuron fires the whole 5s, but firing is still slow and somewhat inconsistent. 1 hour after injection of lorcaserin, the motor neuron fires normally for the whole 5 s.

3-d) Successful treatment of sepsis-induced weakness in rats

Based on a number of experiments, there is an identified defect in persistent inward sodium current causing the inability of motor neurons in septic rats to sustain firing. Persistent sodium current has been studied for years in motor neurons, and it is

known that activation of serotonin receptors (5-HT_{2C}) in the spinal cord increases persistent inward sodium current to allow motor neurons to fire repetitively(15-18). Based on this knowledge, rats that had been septic for 1 day were treated with 3 mg/kg of the selective 5-HT_{2C} agonist lorcaserin. **lorcaserin (trade name Belviq) has an excellent safety profile and is FDA-approved for weight loss(19)**. Using glass microelectrode impalements of single motor neurons for up to 2 hours, the firing pattern before and after intraperitoneal injection of lorcaserin in 4 different rats were recorded (one motor neuron studied per rat; Figure 2). Prior to injection of lorcaserin, motor neurons were unable to sustain steady firing (top trace Fig 2). Fifteen minutes after lorcaserin, motor neuron firing was improved, but still not normal (middle trace Fig 2). One hour after injection of lorcaserin, motor neurons fired normally throughout the 5 second current injection (lower trace Fig 2). There was similar normalization of firing in all 4 motor neurons that recorded before and after lorcaserin injection.

3-e) Drug dosing

The lorcaserin dose that normalizes motor neuron firing in rats is 3 mg/kg delivered via intraperitoneal injection. The human dose for weight loss is 10 mg PO twice daily, but doses up to 60 mg were tolerated in clinical trials. Based on rat-to-human allometric scaling of both pharmacokinetic parameters and 5-HT_{2c} receptor sensitivity (EC_{50}), the 3 mg/kg dose in a rat that fully restored motor unit function is 0.26 mg/kg or 18 mg in a 70 kg adult. Based on doses of lorcaserin that were given to patients prior to FDA approval and rat to human allometric scaling, it appears that treatment of patients with effective doses of lorcaserin is feasible.

3-f) Study Design Rationale

Below, we propose a sequential 2-level dose escalation study of the safety, pharmacokinetics (drug concentration over time) and pharmacodynamics (i.e., muscle strength response) of lorcaserin in critically ill patients with muscle weakness. We selected two different one-time doses of the study drug to provide dose-response data over a range of doses deemed safe for the ICU setting. As described above, these doses are anticipated to bracket (i.e., fall above and below) the anticipated effective dose based on preclinical studies and established differences between species. Observations for drug effect on muscle weakness, adverse events, and drug concentration will be made at specified intervals after each dose (as outlined below). The time between doses, 48 hours, was selected to provide time for the anticipated drug concentrations and muscle strength effects to return to baseline before the second, higher dose

4) Study Procedures

4-a) Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Potentially eligible participants will be identified through screening of the Johns Hopkins Hospital's medical and surgical ICU census (see section 5 for specific eligibility criteria) and IRB approved medical floors under a HIPAA waiver. We will be engaging the CCDA to develop and provide us a daily report of patients on our IRB approved floors who were screened by a treating provider for sepsis and the results of this sepsis screen. Daily reports would be sent to the SAFE virtual desktop. Members of research team who are on this protocol will then review the charts of these patients who had a positive sepsis screen to determine if they meet other inclusion criteria and do not meet exclusion criteria. Potential eligibility will be confirmed by the research team with the patient's attending physician. A treating provider will obtain permission from the patient or surrogate to approach them for a discussion about possible participation in the study.

4-a-1) Informed Consent

Informed consent will be sought for completion of the study eligibility screening and for participation in the study via oral and written consent respectively. Some patients may be incapable of providing informed consent. In such cases, informed consent will be obtained from their surrogate decision-maker. Surrogate decision-makers will be identified as the individual who is making decisions on behalf of the patient for clinical care in the ICU. Consent will be obtained in two steps. First, oral consent will be obtained to perform a brief (< 5 minute) in–bed assessment of muscle strength using a standardized protocol to determine eligibility. Only those patients who are weak, defined either by (a) composite muscle strength sum-score, using Medical Research Council (MRC) scale, <48/60, or (b) a handgrip strength of <11 kg in men and <7 kg in women(2), will be offered written informed consent (since demonstrated muscle weakness is an entry criteria). During the written informed consent process details on the intent of the proposed study, its design, the type of information collected, and potential risks and benefits of participation will be discussed. If surrogates were consented because of the patient's incapability, we will monitor the patient for return of capability and once they are capable, acquire consent from them for continuation in the study.

4-a-2) Planned flow of participants through the study

After consent is obtained, a chart review will be performed to ensure patient still meets eligibility and safety criteria (sections 5 and 4-f, respectively).

4-a-3) Randomization

After informed consent is obtained, eligible patients will be randomly assigned in a 2:1 ratio to the intervention (lorcaserin) or control group (placebo) respectively. (Please see Table 3 and section 4-a-6 for detailed study events.) Group assignment will be masked for patients, clinical and research staff administering the lorcaserin/placebo, and assessing outcomes (muscle strength, safety outcomes, or serum sample collection), as discussed under section 4-c.

4-a-4) Measurement of Exposures and Potential Confounders:

Patient exposures and potential confounders will be collected at study enrollment and are outlined in Table 1. Table 2 summarizes ICU-related exposures and possible confounders that will be collected during the study.

Table 1: Patient-related exposures and potential confounders – Baseline status

Patient Risk Factors	Method for data collection	Measurement Scale
Age/sex/race/ethnicity	Chart review	Continuous/Binary/Categorical
Weight/Height	Chart review	Continuous
Comorbidities: Charlson* & Functional Indices**	Chart review	Ordinal
Severity of illness: APACHE II***	Chart review	Continuous
Leg/Hand dominance	Patient/Proxy interview	Binary
Past Psychiatric History***	Chart review	Categorical

**Charlson Comorbidity index: a score derived from 19 categories of comorbidities, with an increased score reflecting an increased likelihood of one-year mortality(20).*

***Functional Comorbidity Index: An 18 item list of diagnoses which uses physical function as the outcome of interest, with increased score indicative of decreased function(21).*

****Acute Physiology and Chronic Health Evaluation (APACHE II): An index of disease severity that takes into account age, pre-existing medical conditions, and 12 acute physiologic variables that are assessed during the first 24 hours of ICU admission. Scored on a scale from 0-71, with higher scores indicating more severe disease and increased mortality risk(22).*

Table 2: Potential confounders – ICU status

ICU exposure risk factors	Method of Data Collection	Measurement Scale
Sequential Organ Failure Assessment (SOFA) Score**	Chart review	Continuous
ICU admission diagnosis details	Chart review	Categorical

*** SOFA: A composite score that takes into account 6 organ systems used to assess the severity of organ dysfunction in ICU(23), collected on Days 1 and 3.*

4-a-5) Sequence and Timing of Study Events

On Day 1, intervention and control group participants receive 10 mg of lorcaserin or placebo, respectively. Both groups also will undergo assessments before and after administration of lorcaserin/placebo (for assessment details and times, see table 3 and section 4-a-6)

On Day 2, the intervention and control group participants will not receive any lorcaserin/placebo, but will undergo repeat assessments (for assessment details and times, see table 3 and section 4-a-6)

On Day 3, the intervention and control group participants receive 30 mg of lorcaserin or placebo, respectively. Both groups also will undergo assessments before and after administration of lorcaserin/placebo (identical to Day 1).

On Day 4, the intervention and control group participants will not receive any lorcaserin/placebo, but will undergo assessments (identical to Day 2).

4-a-6) Measurements

Participants will be monitored to ensure safety of lorcaserin/placebo administration. This monitoring will include a daily review of interim history (via chart review), medications, and laboratory values (details below), as well as assessment for changes in mental status and monitoring for serotonin syndrome (see table 3).

We also will obtain a battery of outcome measures to test the efficacy in improving muscle strength and assess the safety of lorcaserin, as described in tables 3.

All monitoring will be done by assessors blinded to group allocation.

Table 3: Safety and Efficacy Measures (numbers indicate the number of times within each study day that each measurement is performed)

Measurement	Number of assessments			
	Day 1*	Day 2†	Day 3**‡	Day 4†
Safety Measures				
Chart Review	1	1	1	1
Laboratory Tests (details below)	1	1	1	1
EKG	2	1	1	1
RASS sedation score	2***	1	2***	1
CAM-ICU delirium screen	2***	1	2***	1
Neuro Psychiatric Screen	2	1	1	1
Hunter Serotonin Toxicity Criteria	1	1	1	1

Efficacy Measures				
Handgrip Strength (*Primary Outcome*)	2***	1	2***	1
Arm & leg strength (MMT using MRC Scale)	2***	1	2***	1
Quadriceps Strength using handheld dynamometry	2***	1	2***	1
Lorcaserin serum drug levels[ƨ]	1	1	1	1
Electromyography & Nerve Conduction Study	once only to assess for any peripheral neuromyopathy****			

MMT: Manual muscle strength testing; MRC: Medical Research Council; HHD: Hand-Held Dynamometry; EKG: Electrocardiogram; RASS: Richmond Agitation Sedation Scale; NPI-C: Neuropsychiatric Inventory - Clinician Rating Scale; CAM-ICU: Confusion Assessment Method for the ICU; Hunter Criteria: will be used to evaluate patients for serotonin syndrome (24)

** 10 mg of lorcaserin or placebo administered*

*** 30 mg of lorcaserin or placebo administered*

**** measures are performed as close to the time as drug or placebo administration as possible (within 4 hours) and as soon as possible (between 2 - 6 hours) after drug or placebo administration, on Days 1 and 3 only*

***** EMG & NCS will be performed at any time point after the patient is randomized into study, and will be used to help interpret the results of strength tests*

[ƨ] Peak concentration serum samples will be collected 2 hours ± 15 minutes or 3 hours ± 15 minutes after drug administration (see section 4-a-6.11 for details) and trough concentration serum samples will be collected 24 hour ± 30 minutes after drug administration (see section 4-a-6.11 for details)

† *Days 2 and 4 are consecutive to days 1 and 3 respectively.*

‡ *Day 3 may or may not be consecutive to day 2 depending on assessor availability.*

Safety Measures

4-a-6.1) Chart Review: A daily review of participants' medical records for interim medical history and medications will be performed to monitor for any safety issues and ensure that participants continue to meet eligibility and safety criteria (see sections 5 and 4-f respectively).

4-a-6.2) Laboratory Tests: As indicated in table 3 above, participants will undergo daily blood draws for the following standard laboratory tests: Heme 8 and CMP. In particular, laboratory tests will be obtained prior to every dose of lorcaserin or placebo to ensure that patients meet eligibility and safety criteria (see sections 5 and 4-f respectively). If the relevant tests have already been done for clinical purposes, they will NOT be repeated for research purposes. As these labs are typically measured, at least daily, in the ICU setting, they may not need to be drawn for research purposes and the pre-existing values will be reviewed for research purposes.

4-a-6.3) EKG: Daily EKGs will be obtained to determine if participants develop bradycardia, new-onset QT prolongation (as defined in Section 4.f.3.4 below) or new 2nd or 3rd degree AV block. In particular, this test will be obtained prior to every dose of lorcaserin or placebo to ensure that patients meet eligibility and safety criteria (see sections 5 and 4-f respectively). If this test has already been done for clinical purposes, it will NOT be repeated for research purposes. As this test is commonly done, at least daily, in the ICU setting, it may not need to be done for research purposes and the pre-existing test will be reviewed for research purposes.

4-a-6.4) Richmond Agitation Sedation Scale (RASS)(25): is a validated instrument to measure agitation and sedation status in ICU patients. Participants will be screened for their sedation status daily as well as pre- and post-drug or placebo administration as indicated in table 3 above.

4-a-6.5) Confusion Assessment Method for the Intensive Care Unit (CAM-ICU): The CAM-ICU is a validated delirium screening test for ICU patients. Participants will be screened for their delirium status daily as well as pre- and post- drug or placebo administration as indicated in table 3above.

4-a-6.6) Neuropsychiatric Screening adapted from NPI-C (Neuropsychiatric Inventory-Clinician Rating Scale): NPI-C is a validated instrument used to screen for the presence and severity of symptoms in a number of psychiatric domains, in non-verbal patients, and includes clinician-rating methodology in addition to patient and caregiver inputs(26). Subscales of NPI-C will be adapted to perform daily screening for any hallucinations, delusions, euphoria and agitation in study participants.

4-a-6.7) Hunter Serotonin Toxicity Criteria: Daily physical examinations for serotonin toxicity criteria will be performed using this pre-existing criteria(24) as indicated in table 3 above.

Efficacy Measures

4-a-6.8) Dynamometry of Handgrip Strength (Primary Outcome): Bilateral handgrip strength will be measured pre- and post-drug or placebo administration at time points listed in table 3 above, using a Jamar Plus digital dynamometer in sitting position(27;28)

4-a-6.9) Manual Muscle Strength Testing: Standardized manual muscle testing (MMT) of patients' arm and leg strength using the Medical Research Council (MRC) scale will be measured pre- and post-drug or placebo administration in table 3 above, via physical examination.

4-a-6.10) Dynamometry of Quadriceps Strength: Bilateral quadriceps muscles strength will be measured using a Micro FET Dynamometer in supine position(27;28) pre- and post-drug or placebo administration as indicated in table 3 above. If the patient cannot or will not perform the test for an individual muscle group, the reason for this will be recorded.

4-a-6.11) Serum Drug Levels: Daily blood samples will be collected to determine lorcaserin serum levels by a LC-MS/MS assay and pharmacokinetics. The serum drug samples will be collected and run in at least 2 batches, with the first batch run on specimens after randomization of at least the first 3 patients to lorcaserin (will be done without unblinding the research team regarding the study ID of these subjects). The peak plasma concentration after oral dosing is 1.5 to 2 hours. However, feeding can increase the peak plasma time by 1 hour. Thus, peak concentration samples will be collected at 2hours ± 15 minutes for NPO patients and at 3 hours ± 15 minutes for fed patients. Lorcaserin has a plasma half-life of about 11 hours, and trough concentration samples will be collected at approximately two half-lives, or 24 hours ± 30 minutes.

4-a-6.12) Electromyography (EMG) and Nerve Conduction Studies (NCS):
Nerve conduction will be assessed via the following screening nerve conductions studies in participants after enrolment, to detect potential peripheral neuropathy. NCS results will help us interpret the results of strength tests.

- Motor NCS of bilateral peroneal nerves
- Motor NCS of unilateral ulnar nerve. If ulnar neuropathy at the elbow is diagnosed (slowing of ulnar conduction velocity across the elbow to below 35 m/s or a drop in ulnar motor amplitude of >50% with stimulation above the elbow), Motor NCS of the ulnar nerve of the other extremity will be performed as well.

- Sensory NCS of unilateral ulnar and sural nerves

Motor unit recruitment rate will be assessed via the following EMG studies as well

- EMG of unilateral vastus lateralis muscle
- EMG of unilateral deltoid muscle

If EMG and NCS studies have already been done for clinical purposes, they will NOT be repeated for research purposes, and the pre-existing results will be used for research purposes.

4-b) Study duration and number of study visits required of research participants.

Each participant regardless of group, will be in the study for two 2-day blocks. The detailed timeline of events are detailed in Table 3.

4-c) Blinding, including justification for blinding or not blinding the trial, if applicable.

All participants, clinical staff, and research staff (including those performing outcomes assessments and administering the drug/placebo) will be blinded to the randomization allocation. The investigational pharmacy (which will not be blinded) will prepare the lorcaserin/placebo for administration in similar forms and packaging to prevent unblinding.

If any unexpected, adverse event occurs that may be directly related to the study protocol, unblinding of treatment allocation for that specific participant will occur, as needed, for the principal investigator and IRB (the outcomes assessor(s) would still remain blinded if the patient continued in the trial). Time points and the number of 'unblinding' episodes will be recorded.

4-d) Justification of why participants will not receive routine care or will have current therapy stopped.

All participants, regardless of study group, will continue to receive routine medical care in the ICU. For safety reasons, in consultation with a panel of experts (Drs. Dale Needham – Critical Care; Craig Hendrix – Clinical Pharmacology; Karin Neufeld – Psychiatry, Annette Rowden – MICU Pharmacist), the following procedures were developed and will be followed in the event a participant is scheduled to receive pharmacologic therapies that may potentially interact with the study drug (see Appendices A and B for list of drugs) to minimize the risk of serotonin syndrome or other potential adverse drug effect from CYP2D6 effect on drug metabolism.

1. First, a non-interacting substitute will be sought in consultation with the primary clinical team.

2. In the event that no safe and effective substitute is available, and the interacting agent is classified in
    a. Appendix A, participants will be excluded or withdrawn from the study.
    b. Appendix B participants will not receive more than one other serotonergic agent during the trial, with consideration of the following strategies when/if feasible
        i. In consultation with the participant's clinical team, a decision will be made regarding the safety of temporarily discontinuing a non-essential drug therapy before the start of the 4-day protocol, and restarting the drug at least 2 days (i.e., 4 half-lives of lorcaserin) after the last administration of lorcaserin/placebo.
        ii. If the dosage of any interacting agent (e.g., analgesic) is routinely titrated for desired clinical effect, the clinical team will be informed and cautioned to ensure titration occurs with the consideration for potentiation or decrease in the interacting agent's effect.
        iii. If neither substitution, temporary discontinuation or titration of a potential interacting agent is possible, the patient will be excluded / withdrawn from the study.

4-e) Justification for inclusion of a placebo or non-treatment group.

In our proposed study, patients will be randomized to receive either lorcaserin or Placebo. The FDA-approved drug under study in this trial, lorcaserin, does not have any published data supporting efficacy for muscle weakness in the ICU. Hence, no therapy known to be effective is being withheld from the placebo group. Given that our primary and secondary outcomes are based on semi-objective assessments of muscle strength or subjective assessments of cognitive/psychological symptoms, a control group (with blinded outcomes assessments) is required to reduce bias in patients' outcome assessment. Patients in the control group will continue with routine therapy as deemed appropriate by the clinical team.

4-f) Definition of treatment failure or participant removal criteria.

1. Participants will be removed from this study if the surrogate decision-maker, the patient (when capable of medical decision-making) or the patients' medical team makes a request for removal from the study.

2. As stated in Section 4-d, in the event a participant is scheduled to receive pharmacologic therapies that may potentially interact with the study drug (see appendix A), and substitution, gradual titration or discontinuation of interacting agent is not safe or feasible, within the decision rules outlined in Section 4-d, the participant will be withdrawn from the study.

3. The study drug or placebo will be discontinued for the following physiologic changes. Data collection will continue in these participants.
    1. An increase AST > 8 times the upper limit of normal (ULN)
    2. An increase in ALT > 8 times ULN,
    3. A decrease in creatinine clearance <30 mL/min,
    4. New-onset Q-T prolongation, defined as
        - QTc>500 msec
        - A >60 msec increase in QTc from baseline
    5. New-onset 2nd or 3rd degree heart block without a permanent pacemaker,
    6. Persistent heart rate <60 bpm
    7. New-onset priapism
    8. Serotonin Toxicity (as determined by Hunter Criteria, as previously described)
    9. New-onset psychosis
    10. Onset of new symptoms of hallucinations or euphoria (as determined by NPI-C assessment as described above)
4. If the patient is given a sedative medication during this brief period between baseline and follow-up testing, with a change in mental status that prohibits the ability to perform muscle strength testing, no further testing or administration of lorcaserin/placebo will be done in that patient and a new patient would be recruited and consented in place of this patient.

4-g) Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Those who end their participation in this study prematurely will not be given any further lorcaserin/placebo doses. Similarly, lorcaserin/Placebo administration will cease upon the end of the study. Cessation of lorcaserin will not be harmful to the patient. There are no known adverse effects associated with withdrawal of lorcaserin and there is no need for tapering. Thus its absence or cessation will not directly cause any adverse outcomes. Patient care will continue without change after cessation of lorcaserin/placebo.

5) Inclusion/Exclusion Criteria

5-a) Inclusion Criteria:

1. Age ≥18 years old
2. Sepsis [≥2 Systemic Inflammatory Response Syndrome (SIRS) Criteria AND known or suspected infection]
3. Muscle weakness [Medical Research Council sum score <48/60 or handgrip strength <11 kg in men and <7 kg in women]
4. Obey Commands [Score for DeJonghe Awakening Score of ≥3/5]

5-b) Exclusion Criteria (based on medical record review and discussion with patient/surrogate)

1. Severe renal insufficiency [Creatinine Clearance <30 mL/min – or receiving dialysis]
2. Acute infectious or auto-immune hepatitis, acute liver failure, or a history of cirrhosis without liver transplant
3. History of psychosis
4. Bradycardia, or 2nd or 3rd degree AV block without pacemaker
5. History of valvular heart disease without valve replacement
6. History of priapism
7. Receiving drugs with serotonergic effects and/or CYP2D6 substrates which cannot be substituted stopped or titrated (as described in section 4d).
8. Receiving Sulfonylurea medication at the time of the study
9. Prior neuromuscular or central nervous system disease, including pre-existing neuropathy
10. Inability to perform study's muscle strength assessments based on patient's baseline status prior to hospital admission
11. Unable to receive, or unlikely to absorb, study drug (e.g. bowel obstruction, ischemia, or infarction; short gut syndrome)
12. Body mass index >40
13. Patient not expected to survive >4 days
14. Pregnancy (based on urine or blood test results based on standard practice in the subject's ICU) or lactation
15. Allergy to lorcaserin or lorcaserin taken in the prior 7 days
16. Enrolled in another interventional drug or physical rehabilitation trial
17. Physician declines for patient to be enrolled
18. Patient or proxy declines consent
19. Unable to reach proxy for consent
20. Non-English speaking

6) Drugs/ Substances/ Devices

6-a) The rationale for choosing the drug and dose or for choosing the device to be used.

It is known that activation of serotonin receptors (5-HT_{2C}) in the spinal cord increases persistent inward sodium current to allow motor neurons to fire repetitively, and lorcaserin, as a selective 5-HT_{2C} agonist was used successfully in rat models (see Background, section 3-d)

The lorcaserin dose that normalizes motor neuron firing in rats is 3 mg/kg. The human dose for weight loss is 10 mg PO twice daily, but doses up to 60 mg were tolerated in clinical trials. Based on rat-to-human allometric scaling of both pharmacokinetic parameters and 5-HT_{2c} receptor sensitivity (EC_{50}), the 3 mg/kg dose in a rat is

0.26 mg/kg or 18 mg in a 70 kg adult. Based on doses of lorcaserin that were given to patients prior to FDA approval and rat to human allometric scaling, it appears that treatment of patients with effective doses of lorcaserin is feasible (See Background, section 3-e)

6-b) Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
See attached IND Exemption document

6-c) Justification and safety information if non-FDA approved drugs without an IND will be administered.
Not Applicable

7) Study Statistics

7-a) Primary outcome variable.

The primary analysis will compare the mean change in hand grip strength from baseline to post-drug testing across the 30 mg intervention dose vs. control group using a two-sample t-test.

7-b) Secondary outcome variables.

Secondary analyses will include the following:

1) replication of the primary analysis for the 10 mg intervention dose vs. control group,
2) replication of the primary analysis excluding any patients with neuropathy based on nerve conduction studies (29)within the intervention group,
3) comparison of the change from baseline to post-drug testing across the 10 mg versus 30 mg conditions using a paired t-test
4) a PK-PD analysis for all concentration-strength measures for all observations (across the 4 days) using a traditional Emax model pooling all subjects and all time points.

7-c) Statistical plan including sample size justification and interim data analysis.

The sample size (N=10 for lorcaserin and N=5 for placebo) is a convenience sample to establish preliminary data for a potential larger future study. With alpha = 0.05, power = 80%, and a mean (standard deviation) baseline value of 9 (9) kg for the primary outcome of grip strength, under a 30 mg dose of lorcaserin we could detect a difference of >9 kg for the change in strength from baseline to post-drug testing (on the same day) for the invention group versus no change for the placebo group. This difference represents a 100% increase in strength versus a 400% increase detected with an equivalent dose in the rat model. This calculation assumes that the baseline and post-drug testing measures would be highly correlated (r = 0.8). Under a worst case scenario (i.e., no correlation between baseline and post-drug testing), we could detect at least a 220% increase in strength which is adequate given the large increase expected based on rat models.

7-d) Early stopping rules

There are no early stopping rules for this pilot trial.

8) Risks

8-a). Medical risks, listing all procedures, their major and minor risks and expected frequency.

1) Side effects of Drug / Placebo:

Participants will be closely monitored for any side effects related to administration of the study drug or placebo.

The placebo has no known side effects.

The study drug, lorcaserin, has been extensively studied, has an excellent safety profile and is FDA approved for chronic use for purposes of weight loss(19). The major potential side-effects are listed below. A full list of side effects is available in Appendix C, the FDA prescribing information.

a) Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS) like Reactions: Although lorcaserin has not been associated with any known cases of either serotonin syndrome or NMS, the safety of co-administration of lorcaserin with other serotonergic or anti-dopaminergic agents has not been established.

b) Cardiac valvular and conduction abnormalities: Asymptomatic aortic or mitral regurgitations were seen in patients who were in a randomized control trial of lorcaserin vs placebo for a one-year period, likely due to long-term activation of serotonin receptors on cardiac interstitial cells. In a similar year-long trial of lorcaserin vs placebo, some patients experienced a decrease in their heart rate over time.

c) Cognitive Impairment and Depression or suicidal thoughts: in trials of at least 1 year duration, lorcaserin administration was associated with difficulty with concentration and attention, difficulty with memory and confusion, and some mood problems such as depression.

d) Psychiatric Disorders (including euphoria and dissociation): have been associated with short-term studies of lorcaserin at supratherapeutic dosages.

e) Hypoglycemia was observed in some participants with Type 2 Diabetes on lorcaserin while concomitantly on a sulfonylurea.

f) Priapism: Although lorcaserin has not been associated with cases of priapism, serotonergic drugs like lorcaserin have been associated with priapism.

2) Risk of stopping/adjusting other medications: There may be risks associated with the temporary stopping of other medications

3) EMG and Nerve Conduction Studies: Participants may experience some discomfort. There might also be some bruising in the area where the wire is inserted. Most subjects will not experience any bleeding with the needle studies; even for patients receiving therapeutic anticoagulation, the reported risk of clinically silent hematoma formation is less than 2% (30). If bleeding occurs, no more than a few drops is expected. The risk of infection is extremely small.

4) Blood sampling: Participants may experience discomfort, bruising or bleeding at the site of blood draws. All patients will have blood drawn for research purposes either through indwelling catheters or percutaneously by either a licensed clinical staff or trained research personnel. Risks of percutaneous blood draws are uncommon and include bleeding, discomfort and bruising**.**

5) Chart Abstraction: There is a risk of loss of privacy, since we will be collected data on participants.

6) Strength testing: Participants may feel some tiredness or discomfort in the arm and leg muscles

7) Questions: There is a small chance that a participant could become uncomfortable, bored or fatigued in answering our questions.

8-b) Steps taken to minimize the risks.

1) Side effects of drug/placebo

a) Serotonin Syndrome and NMS-like reactions:
Although this syndrome is rare, the theoretical risk of serotonin syndrome and NMS-like reactions will be mitigated by

i. Monitoring participants for liver and renal failure, which may affect drug levels
ii. Reviewing medication lists to exclude patients on drugs that may cause serotonin syndrome when administered along with lorcaserin (see Appendix A and section 4-d above).
iii. Allowing participants to be on no more than 1 serotonergic agent (plus lorcaserin/placebo) during the trial.
iv. Closely monitoring patients, for toxicity using the NPI-C for mental status changes and Hunter Criteria for Serotonin toxicity.

b) Cardiac valvular and conduction abnormalities:
Patients with a history of valvular heart disease, bradycardia, and 2nd or 3rd degree AV block without pacemaker will be excluded. Participants are unlikely to develop new onset valvular defects given that they will only receive two doses in this trial. Participants will be closely monitored via EKG for bradycardia and new onset 2nd or 3rd degree AV block.

c) Cognitive impairment, Psychiatric Disorders (including euphoria and dissociation) and Depression:
Patients with pre-existing cognitive impairment and psychosis will be excluded. During the trial, patients will be closely monitored using the RASS, CAM-ICU and NPS (Neuropsychiatric screening) instruments.

d) Hypoglycemia: Patients will be excluded if they are receiving a sulfonylurea medication at the time of the study

e) Priapism: this is a theoretical risk will be mitigated by excluding patients with a prior history of priapism, and monitoring during the trial via any noted side effect**.**

2) Risks of stopping/adjusting other medications: These risks will be assessed on a case-by-case basis, in consultation with the participants' medical team.

3) EMG and Nerve Conduction Studies: This is an abbreviated version of a clinical test routinely done, including in the critical care setting. The discomfort to participants is very brief and will not persist beyond the end of this short screening test. The risks of bleeding and infection will be minimized even further by using single-use, small needles, cleaning the area of insertion, and avoiding needle insertion in areas of untreated infection.

4) Blood sampling: Person(s) collecting blood samples will be trained to minimize avoidable discomfort, bruising and bleeding. Most blood will be drawn through indwelling catheters and most of the routine lab work required for this study will already be drawn as part of routine care with little, if any, additional lab work required for this study.

5) Protection of Privacy:
All patient data will be confidential and secure due to physical and electronic data security measures, including locked offices and locked filing cabinets for records and computers, and password protection for computers and electronic data storage. All electronic data will be routinely backed up. Only study staff that are directly involved in data entry, management, or processing, will know the linkage between the unique identifier and participant-identifying information. We will keep all patient information confidential in accordance with Public Health Services Act (42 USC 299a-1(c)).

6) Muscle Strength Testing: We will minimize discomfort of strength testing by monitoring patients and assuring that pre-existing pain is treated before study procedures, by positioning carefully, and by allowing the option to cancel or postpone any assessment, either by subject request or clinical condition**.**

7) Recruitment and Informed Consent
An informed consent process, consistent with the IRB policies and procedures, will be used to enroll each patient for this proposed investigation. It will be emphasized that participation is entirely voluntary and may be discontinued at any time without any impact on the care received during his/her hospital stay. Consent will be documented in writing on an IRB-approved consent form and entered into the medical record, to ensure all ICU providers and nursing staff are aware of the patient's participation.

8-c) Plan for reporting unanticipated problems or study deviations.

The primary investigator (Dr Needham) is a board-certificated critical care physician practicing in the intensive care unit at Johns Hopkins. He will be involved in the daily conduct of the clinical trial and closely supervise the daily screening for patient eligibility, informed consent, and study procedures such outcomes assessments and safety monitoring during the trial. Consequently, immediate knowledge of any unanticipated problem or study deviation that may arise will be available to the P.I. (Dr. Needham) on a timely basis for immediate action and reporting to the IRB as necessary. If Dr. Needham is unavailable, the study will maintain a list of clinicians associated with the study and Dr. Needham's research group who can provide medical guidance.

Administration of lorcaserin/Placebo will be done by licensed clinical staff in coordination with the research pharmacy.

Examples of events that are anticipated in this population of critically ill patients include: transient hypoxemia and hypotension, agitation, delirium, skin breakdown, nosocomial infections, glucose dysregulation, deep venous thrombosis/pulmonary embolus, tube feeding intolerance, cardiovascular compromise, end organ compromise or failure (e.g. renal failure) and death. These events and other similar events, which are often the focus of prevention efforts as part of routine ICU care, will not be considered reportable adverse events unless they are considered by Dr. Needham to be associated with the study protocol. Serious adverse events are defined any untoward clinical events that are:

- Fatal or immediately life threatening
- Permanently disabling or severely incapacitating
- Requires prolonged inpatient hospitalization
- Important medical events that may not result in death, be life threatening, or require prolonged hospitalization may be considered serious adverse events when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the serious outcomes listed above.

If clinically important, unanticipated adverse problems or clinically important study-related, serious adverse events occur, they will be recorded on a designated case report form. All events that are serious and unanticipated, or study-related and adverse will be reported to Institutional Review Board within the required reporting timeline.

8-c) Legal risks such as the risks that would be associated with breach of confidentiality.

All patient data will be confidential and secure due to physical and electronic data security measures, including locked offices and locked filing cabinets for records and computers, and password protection for computers

and electronic data storage. All participant-identifying information will be removed from the dataset before analysis. Only study staff who are required to, will know the linkage between the unique identifier and participant-identifying information. We will keep all patient information confidential in accordance with Public Health Services Act (42 USC 299a-1(c)). There is low risk of a breach of confidentiality.

8-d) Financial risks to the participants.

There are no expected financial risks to the participants

9) Benefits

9-a) Description of the probable benefits for the participant and for society.

There is no direct benefit to participants in this study.

If this trial yields encouraging preliminary data, this would encourage further prospective assessments of lorcaserin using repeat dosing, to establish repeat dosing safety in the ICU and efficacy (i.e., improvement in muscle strength) in critically ill patients with sepsis.

Demonstration of lorcaserin efficacy could result in the first specific drug therapy treating muscle weakness in critically ill ICU patients. Expediting the physical recovery of these patients early in their ICU course has the potential to improve rehabilitation after critical illness. Possible patient benefits could include reduced hospital stays and improved functional outcome. Since lorcaserin is already FDA-approved and on the market with an excellent safety profile (29), success in identifying a biological effect of lorcaserin to improve motor unit function in ICU patients may make translation of these findings into ICU practice more feasible.

10) Payment and Remuneration

10-a) Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will not be paid for participating in this study.

11) Costs

11-a) Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will not be any additional costs to participants beyond routine financial obligations for their hospitalization.

12) Appendices

12-A) Appendix A – List of drugs that if currently administered, will result in exclusion of the participant (details in Section 4-d of eFormA).(31-34). Basis of the exclusion (i.e., either serotonin interaction or CYP2D6 interaction) is indicated.

GENERIC NAME	COMMON NAME	CLASS/GROUP	USE	Serotonin Interaction	CYP2D6 Interaction	NOTES
5-hydroxytryptophan	Oxitriptan / 5-HTP	OTC supplement of a naturally occurring amino acid	Sleep aid - anti depression	Yes		OTC. The interaction reports apply to the OTC supplement form.
Amitriptyline (> 50 mg/day)		TCA		Yes	Yes	
Amphetamine		Stimulant	ADHD - narcolepsy	Yes		
Aripiprazole		Atypical antipsychotic	Psychosis		Yes	
Atomoxetine	Strattera	Norepinephrine reuptake inhibitor	ADHD		Yes	
Brompheniramine		Antihistamine	Common cold and allergic rhinitis	Yes		OTC
Bupropion	Wellbutrin	Aminoketone	Antidepressant	Yes	Yes	
Carvedilol		Beta blocker	CHF-HTN		Yes	
Clomipramine	Anafranil, clofranil	TCA		Yes	Yes	
Clorgiline		Irreversible MAO-A inhibitor	Scientific research	Yes		
Cyclobenzaprine	Amrix, Flexeril, Fexmid		Muscle relaxer	Yes		
Desipramine	Desmethylimipramine	TCA		Yes	Yes	
Dextromethorphan		Morphinan	Cough suppressant	Yes	Yes	Ingredient in many OTCs
Doxepin	Deptran, sinequan	TCA		Yes	Yes	
Flecainide	Tambocor	Class Ic antiarrhythmic	Tachyarrhythmia		Yes	
Fluoxetine		SSRI		Yes	Yes	
Furazolidone		Antibacterial		Yes		
Ginseng		Plant	Energy drinks - herbal teas	Yes		
Hypericum perforatum	St. John's wort	Plant	Herbal treatment for depression	Yes		
Imipramine		TCA		Yes	Yes	
Isocarboxazid		Irreversible MAO inhibitor	Mood disorders	Yes		
Linezolid	Zyvox	Antibiotic		Yes		
Lofepramine		TCA	Antidepressant	Yes		
L-tryptophan	Dietary supplement	One of the 22 standard AA essential AA in human diet	Dietary supplement	Yes		OTC. The interaction reports apply to the OTC supplement form.
Methadone		Opioid	Analgesic - maintenance anti-addictive	Yes		
Metoclopramide		Dopamine-receptor antagonists	Treat nausea and vomiting	Yes		
Mexiletine	Mexitil	Class Ib anti-arrhythmic			Yes	
Moclobemide		Reversible MAO-I		Yes		Not USA approved yet
Nortriptyline		TCA	Depression - nocturnal enuresis - chronic pain	Yes		

Paroxetine		SSRI		Yes	Yes	
Peganum harmala	Esfand, Syrian rue, harmel	Plant		Yes		
Pentazocine		Mixed agonist–antagonist narcotic	Analgesic	Yes		
Phenelzine		MAO-I	Antidepressant	Yes		
Procarbazine		Antineoplastic chemotherapy drug	Hodgkin's lymphoma	Yes		
Propoxyphene		Opioid	Analgesic	Yes		
Ritonavir	Norvir	Protease inhibitor	HIV/Aids	Yes		
Selegiline		Irreversible MAO-I	Parkinson/depression/dementia	Yes		
S-metoprolol		Beta blocker			Yes	
Tamoxifen		Agonist-antagonist estrogen	Cancer		Yes	
Thioridazine		Typical antipsychotic			Yes	
Timolol		Beta-adrenergic receptor antagonist	Glaucoma - HTN - Migraine		Yes	
Tramadol	Ultram	Opioid	Pain	Yes	Yes	
Tranylcypromine	Parnate	Irreversible MAO-I	Depression - anxiety	Yes		

12-B) Appendix B – List of drugs that if currently administered, will require physician approval for participant to be included in the study (details in Section 4-d of eFormA).(31-34)

GENERIC NAME	COMMON NAME	CLASS/GROUP	USE	Serotonin Interaction	CYP2D6 Interaction	NOTES
Codeine	3-methylmorphine	Opiate	Analgesic		Yes	
Duloxetine	Cymbalta	SNRI	MDD - GAD	Yes	Yes	
Haloperidol	Haldol	Typical antipsychotic			Yes	
Risperidone		Atypical antipsychotic			Yes	
Venlafaxine	Effexor	SNRI		Yes	Yes	
Amitriptyline (≤ 50 mg/Day)		TCA		Yes	Yes	
Bromocriptine	Parlodel, Cycloset	Ergoline Derivative - Dopamine agonist	Pituitary tumors - Parkinson's - Hyperprolactinemia - NMS	Yes		
Buspirone	Buspar	Azapirone	anxiolytic	Yes		
Carbamazepine			Anticonvulsant	Yes		
Chlorphenamine	Chlorpheniramine, piriton	Antihistamine	Allergies	Yes		
Citalopram	Celexa, cipramil	SSRI		Yes		
Dextropropoxyphene		Opioid	Analgesic	Yes		
Escitalopram	Lexapro, cipralex	SSRI		Yes		
Fentanyl	Fentanil	Opioid	Analgesic	Yes		Including the patch (Duragesic)
Fluvoxamine		SSRI		Yes		
Granisetron	Kytril	Antiemetic	After chemo	Yes		
Lithium		Element	Bipolar disorder	Yes		
Meperidine	Pethidine	Opioid	Analgesic	Yes		

Milnacipran	Ixel, savella, dalcipran, toledomin	SNRI	Fibromyalgia	Yes		
Mirtazapine		NaSSA	Antidepressant	Yes		
Nefazodone	Dutonin, nefadar, serzone	SNDRI	Antidepressant	Yes		
Sertraline		SSRI		Yes		
Tapentadol	Nucynta	Opioid	Analgesic	Yes		
Toloxatone	Humoryl	Antidepressant		Yes		
Trazodone		Serotonin antagonist and reuptake inhibitor	Antidepressent	Yes		
Triptans (controversial)	Sumatriptan, rizatriptan, naratriptan, eletriptan, almotriptan, frovatriptan, avitriptan, zolmitriptan			Yes		
Valproate	Valproic acid	Anticonvulsant	Anticonvulsant/mood stabilizer	Yes		
Ondansetron	Zofran	Serotonin 5-HTa receptor antagonist	Antiemetic	Yes	Yes (minor)	
Oxycodone		Opioid	Analgesic		Yes (minor)	
Propafenone		Anti-arrhythmic medication			Yes (minor)	

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