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Daily quetiapine after severe TBI improves learning and memory

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Author Contribution

PB: literature search, study design, data interpretation, writing, critical revision experimental procedures, data collection, data analysis, data interpretation, writing, critical revision. AT: experimental procedures, data collection, data analysis, data interpretation, writing, critical revision. MC: literature search, study design, data interpretation, critical revision. MCC: experimental procedures, data collection, data interpretation, critical revision. PS: study design, experimental procedures, data analysis, data interpretation, writing, critical revision. PMQ: data interpretation, critical revision. APG: experimental procedures, data collection, data interpretation, critical revision. EA: experimental procedures, data collection, data interpretation, critical revision. KDB: experimental procedures, data collection, data interpretation, critical revision. CJ: experimental procedures, data analysis, data interpretation, critical revision. LJK: data interpretation, critical revision. DFM: data interpretation, critical revision. DHS: data interpretation, critical revision. JLP: literature search, study design, data collection, data analysis, data interpretation, writing, critical revision.

ABSTRACT

BACKGROUND: Traumatic brain injury (TBI) induces cognitive deficits driven by neuroinflammation and cerebral edema. The commonly used atypical antipsychotic, quetiapine (QTP), has been recently shown to improve post-TBI outcomes. We hypothesized that QTP would thereby improve animal learning and memory 2 weeks after severe TBI.

METHODS: CD1 male mice (n=35) underwent severe TBI (controlled cortical impact, injury, I) or sham craniotomy (S), followed by BID saline (P, placebo) or QTP (10 or 20 mg/kg, IP) for 2 weeks. Animals underwent Morris Water Maze (MWM) exercises to gauge spatial learning and memory. The distance and time required for swimming animals to reach the platform area (Zone 5, Z5) located in quadrant 1 (Zone 1, Z1) was calculated from digital video recordings analyzed using Ethovision software. Animal bodyweights were recorded daily and on day 14, injured cerebral hemispheres were procured for edema determination (wet-to-dry ratio). Intergroup differences were evaluated with ANOVA/Bonferroni correction ($p<0.05$).

RESULTS: On day 14, animal weight loss recovery was lowest in I+P compared to I+QTP20 and I+QTP10 ($p\leq0.01$ for either). Cerebral edema was greatest in I+P, and only significantly decreased in I+QTP20 ($p<0.05$). Both QTP doses similarly improved spatial learning by significantly reducing latency time and travel distance to target zones ($p<0.05$). In probe memory trials, only I+QTP20 and not I+QTP10 significantly favored animal reaching or crossing into target zones ($p<0.05$).

CONCLUSION: Post-TBI QTP reduces brain edema and improves spatial learning and memory with a potential dose dependence impact benefiting memory up to 14 days. These data suggest an unanticipated QTP benefit following brain injury that should be specifically explored.

KEY WORDS: Learning; memory; Morris Water Maze; quetiapine; traumatic brain injury.

Regardless of mechanism, traumatic brain injury (TBI) disrupts normal cerebral function and drives both emergency care and long-term care depending on severity. In 2014, the CDC recorded 2.53 million emergency department (ED) visits related to TBI. This encompassed approximately 288,000 TBI-related hospitalizations and 56,800 TBI-related fatalities, spanning all age groups.[1] Despite advancements in basic and translational research that have reduced TBI mortality rates, TBI remains a leading cause of disability among young individuals. The dearth of effective post-injury therapeutic interventions has resulted in prolonged intensive care unit (ICU), hospital and long-term care facility dependence. Subsequent convalescent care exerts a significant financial strain on health systems and families tasked with providing lifetime care.[2,3] While initial tissue impact result in primary brain injury, ultimate outcomes are more significantly influenced by events and pathophysiological occurrences in the hours and days following the injury. These potentially avoidable events including hypoxemia, hyperglycemia, and hypercarbia for example, collectively lead to secondary brain injury.[4] The deleterious influences of secondary brain injuriants are expressed through incompletely understood mechanisms but include inflammatory, excitotoxic, and apoptotic processes.[5] Neuroinflammatory events, involving glial cell activation and neutrophil trafficking, augment the upregulation of local and regional inflammatory mediators.[6] Modulating undesirable inflammation offers promise as a therapeutic approach to mitigate against secondary brain injury to improve both functional and cognitive outcomes.[7,8]

The administration of typical or atypical antipsychotic agents such as quetiapine (QTP) to treat agitation or delirium occurs frequently after TBI as well as other critical illnesses or injuries. Besides behavioral control and delirium management, such agents have been shown to potentially reduce post-TBI cerebral inflammation and edema and enhance

outcomes.[9–11] In contrast to the wealth of information in preclinical models, there is limited human investigation linking antipsychotic therapeutics with post-TBI or post-stroke outcomes.[12] In a short term (54 hours) *in vivo* investigation, our group demonstrated a compelling correlation between escalating doses of QTP, and a consistent decrease in blood brain barrier leukocyte mobilization and microvascular permeability as observed *in vivo,* in a penumbral region 54-hours after severe TBI.[9] Additionally, escalating QTP doses better normalized 48-hour Garcia neurological test (GNT) scores, injured cerebral hemisphere water content (edema), and animal body weight loss recovery. This data suggests an acutely beneficial role for QTP in reducing cerebral inflammation and edema. The impact of QTP therapy on longer term outcomes including cognitive recovery affecting learning and memory, remains uncertain but worthwhile investigating. We therefore hypothesized that QTP administration would enhance cognitive recovery for weeks after an initial severe blunt TBI by improving learning and memory in a durable fashion.

MATERIALS AND METHODS

Experimental Design and Study Groups

The procedures described below received pre-investigation approval from the University Institutional Animal Care and Use Committee. The ARRIVE Checklist was followed, completed and submitted as Supplemental Digital Content, http://links.lww.com/TA/D862.[13] Adult male CD1 mice weighing 25-32 grams (Charles River Laboratories, Wilmington, MA), were acclimated in standard housing facilities with alternating dark and light cycles and access to both water and chow *ad libitum*. On day 0, mice were randomized to one of two procedures: sham craniotomy (Sham [S]) or severe TBI induced by controlled cortical impact (CCI, Injury [I]) (details below; Fig. 1).

Immediately following TBI, mice were further randomized to receive twice daily intraperitoneal injections (IP) of 0.3ml of either 0.9 % normal saline (NS, Placebo [P]) (Baxter Healthcare Corporation, Deerfield, IL) or quetiapine hemifumarate (QTP; Sigma Aldrich, St Louis, MO) as a low (10mg/kg) or high dose (20mg/kg). Uninjured sham craniotomy mice received either NS or 20mg/kg of QTP IP. These dosing regimens were administered for 14 days and based on previously validated reports focusing on the neuroprotective effects of QTP that established equivalence with oral QTP administered to humans in the ICU[14,15].

Thirty-five (35) mice were randomly allocated to one of five groups (n=7/group). (1) Sham craniotomy and NS BID **(S+P)**; (2) Sham craniotomy and QTP 20mg/kg BID **(S+QTP20)**; (3) CCI and placebo BID **(I+P)**; (4) CCI and QTP 10mg/kg BID **(I+QTP10)**; (5) CCI and QTP 20mg/kg BID **(I+QTP20)**. Group sample size was chosen by convenience sampling which was informed by prior studies conducted in our laboratory that employed the same Morris water maze experiments and data analysis methods.[16,17]

Murine Severe TBI Model

Controlled cortical impact (CCI) is a well-established murine injury model that reproduces severe TBI.[18] On day 0, rodents were induced and maintained under anesthesia with inhalational isoflurane (3.5 % induction followed by 2% maintenance) throughout the surgical procedure. Subcutaneous bupivacaine (Fresenius Kabi, Lake Zurich, IL; 0.5mg/mL) and buprenorphine-SR (Zoopharm, Laramie, WY; 1mg/kg) were then injected to provide extended analgesia. Mice were then positioned prone within a stereotactic frame, and a circular 4mm-diameter tracing was marked on the skull between the left bregma and lambda sutures using a trephine. A craniotomy was created with a dental drill (Henry Schein,

Melville, NY) and the bone flap was removed. The dura mater was carefully preserved without injury. In TBI animals, a controlled cortical impactor (AMS201, AmScien Instruments, Richmond, VA) imparted a standardized severe TBI injury to the exposed left parietocerebral cortex, employing the following validated parameters: 3mm-diameter impactor tip, impact velocity of 6m/s, and cortical deformation depth of 1mm.[18] The scalp was sutured closed once hemostasis was achieved.

Body Weight Loss Recovery

Animal body weights were measured both prior to the craniotomy (W0) and daily for the subsequent 14 days. Animal weight loss was calculated relative to the initial animal body weight (W0) and expressed as a percentage using the following formula: ([W0-Wx] / W0) × 100%, where 'x' represents the number of days after the CCI or sham craniotomy.

Brain Tissue Water Content

After the completion of Morris water maze trials on day 14, animals were euthanized, and their brains and lungs extracted. Each brain hemisphere was extracted separately and labeled as the injured (ipsilateral) or uninjured (contralateral) hemisphere. Hemisphere wet weight (WW) was measured immediately upon organ removal and dry weight (DW) was determined after 72 hours of dehydration at 70 ℃. The percentage of tissue water content was calculated using the wet-to-dry ratio formula: % water content = 100 × [(WW-DW) / WW].

Morris Water Maze

Starting on day 6, mice underwent a series of daily exercise trials in a Morris water maze (MWM) by one author (AT) who was blinded to treatment and group allocation (Fig.

2). The water maze consists of a 100 cm diameter circular pool filled with water at a constant temperature of 22°C. The tub is divided into four equal quadrants with a 10cm diameter escape platform positioned in the center of the north quadrant, termed Zone 1. Additional concentric zones around the escape platform were demarcated with the following diameters: Zone 5 (10 cm), Zone 6 (18 cm), Zone 7 (24 cm), and Zone 8 (32 cm). Zone 5 was the 10-cm area surrounding the platform, regardless of whether the platform was present, below the surface, or absent. Exercises included a mix of standard cued, spatial, and probe trials.

Cued Learning Trials

Over the course of days 6 and 7, mice participated in four cued trials daily to help them associate reaching the platform with a positive outcome. The platform's location was randomized within one of the four quadrants and marked with a flag at its center for visibility (Fig. 2). Elevated 1 cm above the water level, the platform was visible to the swimming mice, but no other visual cues on the pool walls were provided. The aim of these trials was to acclimate the mice to the MWM and train them to recognize the platform as the objective.

Mice were randomly positioned facing away from the center at varying starting points (north (N), east (E), south (S), west (W)), and given a 60-second window to locate and swim onto the above water and dry platform. If a mouse failed to reach the platform within the allocated time, the operator guided it onto the platform, allowing it to remain there for 15 seconds before removing it from the MWN and drying it off. The mice were subsequently placed under a heat lamp and given a 10-minute rest period between trials.

Spatial Learning Trials

On days 9 through 13, mice were subjected to daily spatial learning trials (4

trials/day). In these trials, the platform was only positioned in the north quadrant (Zone 1) of the pool but was submerged 1 cm below the water surface and was devoid of an identifying flag rendering it invisible to the swimming animal. However, distinctive visual markers were strategically placed on the inner walls of the water tub at each cardinal point (N, S, E, W) along the pool's perimeter. These markers served as navigational cues for the mice to learn and locate the submerged platform.

The objective of these spatial learning trials was to evaluate mouse capability to employ visual cues for navigation to reach the hidden platform. The starting position for each trial was randomly varied to prevent the mice from identifying the platform's location prior to entering the MWM.

In each spatial learning trial, mice were allowed 60 seconds to locate and reach the platform. Upon reaching the platform, tracking was stopped. Failure to reach the platform within 60 seconds led to the mouse being manually prodded onto the platform, where it remained for 15 seconds before extraction and placement under a heat lamp for a 10-minute recovery period before the next trial.

Probe Memory Trials

The final series of trials were the probe memory trial that took place from days 9 to 14, occurring once per day following spatial trials on days 9-13, and 4 times on day 14. During probe trials, the platform was removed, but pool wall spatial cues remained unchanged from the spatial trials. These trials aimed to evaluate long-term memory of the platform's location solely using visual cues. Animals were released from varying starting points along the pool's perimeter and allotted a maximum of 30 seconds to swim to the

platform's location, after which they were removed from the water.

All MWM mouse trials were video recorded using an overhead camera and analyzed with Ethovision software (Ethovision, Noldus, Leesburg, VA). Parameters such as time latency to reach a platform/zone, swimming distance covered to reach the platform/zones, time duration in a given zone and crossing frequency into a given zone (number of times) were collected.

For cued trials, total distance moved (cm), trial time (s), and mean swimming velocity (in cm/s) were collected. During spatial trials, latency to and distance travelled to reach Zones 1, 7, and 8 were assessed. Duration and frequency in Zone 5 were not measured during spatial trials due to the presence of the platform in that zone, although mean distance to Zone 5 was quantified. In probe trials, the following metrics were measured: latency to, distance travelled, as well as the time spent in and crossing frequency into Zones 1, 5, 7, and 8 were collected. Additionally, the mean distance to Zone 5 was calculated.

Statistical Analysis

Data are presented as mean ± SEM and were processed in Prism (GraphPad Software, San Diego, CA, 2022). Group differences were analyzed using ANOVA with Bonferroni correction for multiple group comparisons. Significance was assumed for $p < 0.05$.

RESULTS

Body Weight Loss Recovery

The degree of initial weight loss, the extent of subsequent weight recovery, and the rate of weight recovery indicate neurological and systemic recuperation from operative

procedures and TBI. S+P animals consistently recovered more body weight than I+P counterparts (Fig. 3A). The slope of both I+QTP groups' weight loss recovery is more acute than the I+P curve indicating a more rapid recovery of body weight over time. Cumulative body weight changes on day 14 significantly favored I+QTP20 which reached levels similar to S+QTP20 (Fig. 3B). All animals subjected to experiments in any of the groups survived.

Tissue Water Content

Assessing sham or CCI cerebral hemisphere (ipsilateral to the craniotomy) day 14 edema, the greatest water content was found in untreated injured mice (I+P: 77.2 ± 0.63%; Fig. 4). Expectedly, significantly less water content was found in S+P (74.5 ± 0.63%, p=0.001) as well as QTP treated mice - but only at the higher dose (I+QTP20; 74.9 ± 0.63%, vs. I+P, p=0.01). The water content of cerebral hemisphere contralateral to the craniotomy or of lungs did not exhibit notable intergroup differences among all the injured groups, regardless of treatment or dose.

Morris Water Maze Exercises

Cued Learning Trials

There were no significant intergroup differences across groups in any of the measured parameters that were assessed during the cued learning trials.

Spatial Learning Trials

In spatial trials, all injured QTP-treated mice significantly outperformed the I+P control mice in latency to reach target zones. I+QTP10 mice demonstrated significantly lower Zone 1 latency (I+QTP10 vs. I+P: 6.2±0.4s vs. 8.6±0.6s, p=0.02) but also reduced latency to

the platform zone (Zone 5; Fig. 5A). Both I+QTP groups similarly outperformed I+P (20.9±1.5s) in latency to Zone 7, (I+QTP10: 14.1±1.1s, $p<0.01$; I+QTP20: 13.4±1.2s, $p<0.001$) and Zone 8 (Fig. 5B).

During spatial trials, the I+QTP groups swam consistently closer to the platform compared to I+P mice. Both I+QTP groups demonstrated a reduced mean distance to Zone 5 (Fig. 5C).

Both I+QTP10 (2.6±0.1, $p<0.0001$) and I+QTP20 (2.2±0.1, $p<0.01$) mice crossed into Zone 7 more frequently than I+P mice (1.7±0.1).

In all spatial trials, no significant differences were detected among any of the injured groups in the other spatial parameters (mean velocity, duration in/frequency in Zone 1, duration in Zone 7, and duration in/frequency in Zone 8). In no spatial trial parameter were the QTP-treated injured groups significantly outperformed by I+P.

Probe Memory Trials

Only I+QTP20 mice exhibited lower latency to Zone 1 than I+P mice (6.3±0.6s vs. 9.6±1.0s, $p=0.02$). This shorter latency time only of higher dose treated animals (I+QTP20) was also noted for Zone 7 (Fig. 6A) and Zone 8 (Fig. 6B).

Only I+QTP20 mice demonstrated significantly higher frequent crossing into Zone 8 (Fig. 6C). Both I+QTP10 (3.4±0.2, $p=0.046$) and I+QTP20 (3.8±0.2, $p<0.001$) mice exceeded I+P (2.7±0.2) in Zone 1 crossing frequency.

In probe trials, no significant differences were detected among any of the injured groups in the other measured probe parameters (mean velocity, duration in Zone 1, mean distance to/duration in/frequency in/latency to Zone 5, or duration in/frequency in Zone 7 and duration in Zone 8). In no probe trial parameter were any QTP-treated injured group significantly outperformed by I+P.

In summary, memory was poorest in I+P animals and though, in some cases, both QTP doses improved results; a more generalized finding was that only higher dose (I+QTP20 but not I+QTP10) lead to significantly improved performance when compared to untreated injured animals.

DISCUSSION

In this study, we characterized the impact of post-TBI QTP dosing on learning and memory recovery. Daily QTP for 2 weeks improved markers of spatial learning regardless of dose, while only higher dose QTP appeared to principally enhance memory recovery. The latter dose response benefit was also observed in other post- TBI outcomes including animal weight recovery and reduced cerebral edema.

Quetiapine fumarate, is a dibenzothiazepine derivative and second-generation atypical antipsychotic commonly utilized in the management of ICU delirium and psychosis.[19] It is also routinely employed in various psychiatric conditions, including schizophrenia and bipolar disorder, exhibiting a strong affinity for the serotonergic 5HT2-A/5HT1-A receptors but also interacting with D1/D2 (dopamine), H1 (histamine), and α1/α2 (norepinephrine) receptors.[20,21] Mechanistically, quetiapine appears to demonstrate immunomodulatory activity as it blunts catecholamine (dopamine, serotonin and norepinephrine) downstream

activity, reduces cerebral tissue inflammation.[22]

Broad evidence underscores quetiapine's potential for cognitive enhancement in psychiatric contexts. An open-label QTP study involving patients with borderline personality disorder showed improvements in spatial learning, word fluency, and problem-solving skills.[23] Likewise, in patients with schizophrenia, enhancements in motor skills, attention, and executive functioning were observed after an eight-week course of quetiapine.[24] Head-to-head comparisons between several atypical antipsychotic agents demonstrated greater improvements in cognitive function over one to two years in patients with schizophrenia.[25,26] In a post-traumatic syndrome disorder (PTSD) rodent model, QTP blunted anxiety-like behavior and cognitive impairments.[27] In multiple sclerosis, quetiapine reduced murine brain TNF-α and IL-6, reduced activated astrocytes and microglia abundance, and attenuated CD4 T-cell while upregulating Treg cell infiltration.[28,29] Finally, in patients with Parkinson's but not Alzheimer's, significant cognitive recall improvements were noted following QTP therapy[30] In our study, twice daily QTP for 2 weeks after injury, globally improved clinical recovery demonstrating murine improvement in learning where the platform was hidden and remembering where the platform had been after removal in the probe trials. Unexpectedly, cerebral edema in the craniotomy hemisphere as measured so long after injury - on day 14 - remained also reduced by QTP but only at the higher dose, corroborating previous parallel findings (*in vivo* and *ex vivo*) at 54 hours after injury.[9] This body of evidence underscores quetiapine's potential utility as a cognitive support agent for patients with well-defined neurologic conditions and suggests a role following TBI.

A recent retrospective analysis of quetiapine treated post-TBI patients noted a 25% reduction in in-hospital mortality and an improvement in median discharge Glasgow Coma

Scale compared to matched controls.[11] The authors further reported how higher dose quetiapine patients who underwent intracranial pressure (ICP) monitoring demonstrated lower intracranial pressure (ICP) and higher cerebral perfusion pressure (CPP). Since high ICP and low CPP appear to worsen post-TBI outcomes, quetiapine may serve as an important adjunct therapy for those with the most severe TBI. Unfortunately, how this human study's low and high quetiapine dosage compares to the IP doses administered in our murine model is difficult to interpret and draw any correlation other than an interesting similarity. Similarly, quetiapine appears to improve neurobehavioral outcomes by reducing irritability and aggression in those with TBI complicated by delirium.[31-33] Moreover, there is a suggestion that quetiapine may also enhance downstream cognitive function and neuropsychological in the humans tested.[32]

In animal studies, certain evidence also points to quetiapine's advantage after TBI. In one animal CCI model, exposure to a typical antipsychotic (Haldol) resulted in worsened TBI-induced motor and cognitive deficits but this was not found when exposing animals to quetiapine (atypical) instead.[34] Using MWM exercises, however, the authors were unable to demonstrate significant QTP-related improvements in spatial learning or probe memory trials. However, the study's QTP dosing frequency was daily not twice daily as in our study, potentially pointing to relative underdosing for the lack of observed effect. Additionally, in contrast to our study, only three MWM parameters were evaluated as opposed to the five individual parameters (latency time, duration, frequency of crossing, distance covered, velocity) collected in our study and evaluated in 5 concentric zones (not only 2), potentially missing capture of subtly altered learning/memory differences between groups. Interestingly, in the group receiving daily QTP (10mg/kg once daily) spatial learning (z5 latency) on day 14 approached that of sham levels, a finding similar to those same specific findings in our

study. Specifically in probe trials, our study noted that only higher dose (I+QTP20) animals demonstrated memory improvements suggesting that there is a dose dependent effect or a threshold effect in memory recovery for quetiapine therapy. Leveraging the additional granularity of our analysis highlighted that I+QTP mice consistently outperformed I+P counterparts in a majority of parameters analyzed. In 2 additional rodent studies, while typical antipsychotics (i.e. haloperidol) administered after TBI consistently resulted in delayed cognitive recovery, this was not found with atypical antipsychotics.[35,36] Unfortunately, while these studies also utilized MWM exercises, none of them specifically tested quetiapine.

Different mechanisms can be speculated for the observed quetiapine-related improvements in cognition, learning and memory after TBI. Quetiapine has been found to blunt oxidative metabolism (reducing MDA and elevating GSH brain homogenate levels), reduce neuronal inflammation (lower homogenate COX-2, NF-κB, and TNF-α), and affect apoptosis, altering secondary neuronal tissue injury in central and spinal cord injury models.[37,38] Quetiapine also appears to profoundly reduce myeloid cell line activity, particularly blunting activation and trafficking numbers of neutrophils and macrophages.[39,40] Using an identical CCI murine model as in the current study but coupled with intravital microscopy conducted 54 hours after injury, our group recently reported that incrementally increased QTP dosing reduced leukocyte mobilization to penumbral cerebral tissue at 2 days post-TBI.[9] These stepwise and rapid parallel changes with increased post-TBI QTP dosing were associated with incrementally improved Garcia Neurological Test scores at 24 and 48 hours as well. Quetiapine similarly enhanced *in vitro* rodent rat brain microvascular endothelial cell (BMEC) permeability in another study, corroborating these *in vivo* findings and pointing to a quetiapine-related preservation of the endothelial blood brain barrier after TBI.[10]

Relatedly, utilizing the same murine CCI model as ours, these authors demonstrated that quetiapine completely abrogated *in vivo* blood brain barrier leakage of FITC-dextran up to 70 minutes after TBI.[10] The current study, however, was not designed to explore the mechanism of action but did confirm consistent QTP-related improvements in surrogates of neurological recovery, enhancing both learning and memory in rodents.

While the current study provides insights into quetiapine-driven learning and memory enhancement in brain-injured mice after severe TBI, there are important limitations to discuss. The murine model employed in this study exclusively utilized CD1 male mice precluding the evaluation of sex-based outcome differences. Based upon our use of this specific mouse strain and sex for over a decade, a consistent approach supported linkage across related inquiries. Nonetheless, the data may not be extrapolatable to female mice especially since TBI and certain neuroprotective strategies affect females and males quite differently.[41,42] Additionally, we refrained from investigating known electrophysiologic side effects of quetiapine, such as QTc prolongation and development of *torsade de pointes*, as our study focused on behavior related to learning and memory. This decision was made to ensure that daily memory and learning tests were not disrupted by additional animal activity or neurologically active medications as obtaining electro cardiac tracings involve mouse sedation. Nonetheless, no animal suffered cardiac arrest even during vigorous activity (i.e. swimming). We pursued only two quetiapine doses and may have therefore missed a threshold for benefit at an even lower dose. While 14 days is relatively long for a murine study after TBI, any potential benefits of the lower quetiapine dose that could manifest at a later follow-up period were not captured. Indeed, QTP may simply have accelerated normalization of certain parameters being manifestly improved over placebo within the 14-day experimental observation window but there is no way of knowing if followed

indefinitely, any or all studied parameters would have normalized in all groups with time. Furthermore, murine days are not equivalent to human days[43], thus treatment or learning/memory testing exercises in mice for 14 days is not equivalent to 2 human weeks but likely a much longer time, making timeframe inferences difficult to quantify. Also, we did not assess long-term impact of quetiapine assisted recovery on other murine social behaviors such as foraging, mating or behavior within a group social structure. While QTP and other atypical antipsychotics are not routinely utilized to provide pain control, all have been noted to have potential analgesic properties. There is no way of knowing if the improved MWM performance in QTP-treated groups was specifically from better pain control. Finally, as a mouse study, the study is not directly extrapolatable to humans, but provides additional preclinical information that may help shape human investigation.

CONCLUSION

Our study demonstrates that two weeks of post-severe TBI quetiapine improves both spatial learning and memory in mice. Memory, in particular, seems enhanced at a higher dose of quetiapine while spatial learning appears devoid of similar benefit. The ability of quetiapine to support recovery of cognitive function following TBI offers the potential for early intervention that may demonstrate durable beneficial effects.

SUPPLEMENTAL DIGITAL CONTENT

SDC 1. Author COI forms.

SDC 2. ARRIVE checklist.

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LEGEND OF FIGURES

Figure 1. Experimental timeline.

Figure 2. Morris water maze (MWM) trials overview and setup. (A) Cued Learning Trials (Days 6-7): The platform is above water and mice have 60s to reach the platform. (B) Spatial Learning Trials (Days 8-13): The platform, submerged and not visible. Distinct visual markers at cardinal point pool walls serve as the cues. (C) Probe Memory Trials (Days 9-14): The platform is removed, but the spatial cues are retained.

N, E, S, W, north, east, south, and west mouse starting positions, respectively.

Figure 3. (A) The daily average percentage change in animal body weight over the course of 14 days following either a sham craniotomy or CCI. (B) More detailed representation of panel A, specifically focusing on Day 14 summative results.

S, sham craniotomy animals, I, injured animals; S+P, sham craniotomy followed by NS; S+QTP20, sham craniotomy followed by QTP 20mg/kg; I+P, CCI (injury) followed by NS treatment; I+QTP10, CCI followed by QTP 10mg/kg; I+QTP20, CCI followed by QTP 20mg/kg.

Figure 4. Organ tissue water content. Ipsilateral (injured) cerebral hemisphere. Tissue water content measured by wet-to-dry ratios (↑% tissue water = ↑ edema).

S, sham craniotomy animals; I, injured animals; S+P, sham craniotomy followed by NS; S+QTP20, sham craniotomy followed by QTP 20mg/kg; I+P, CCI (injury) followed by NS treatment; I+QTP10, CCI followed by QTP 10mg/kg; I+QTP20, CCI followed by QTP 20mg/kg.

Figure 5. Comparative analysis of spatial navigation in animals post treatment. (A) Spatial Mean Distance to Platform: The average distance animals were from the platform during each trial of the experiment. (B) Spatial Latency to Zone 5: The amount of time in seconds it took animals to enter Zone 5. (C) Spatial Latency to Zone 8: The amount of time in seconds it took animals to enter Zone 8.

S+P, animals with sham craniotomy followed by NS treatment; S+QTP20, animals with sham craniotomy treated with QTP 20mg/kg; I+P, animals that underwent CCI followed by NS treatment; I+QTP10, animals that underwent CCI and were treated with QTP 10mg/kg; I+QTP20, animals that underwent CCI and were treated with QTP 20mg/kg.

Figure 6. Comparative analysis of probe navigation in animals post treatment. (A) Probe Frequency in Zone 8: The number of times animals entered the border of Zone 8. (B) Probe Latency to Zone 8: The amount of time in seconds it took animals to enter Zone 8. (C) Probe Latency to Zone 7: The amount of time in seconds it took animals to enter Zone 7.

S+P, animals with sham craniotomy followed by NS treatment; S+QTP20, animals with sham craniotomy treated with QTP 20mg/kg; I+P, animals that underwent CCI followed by NS treatment; I+QTP10, animals that underwent CCI and were treated with QTP 10mg/kg; I+QTP20, animals that underwent CCI and were treated with QTP 20mg/kg.

Figure 1

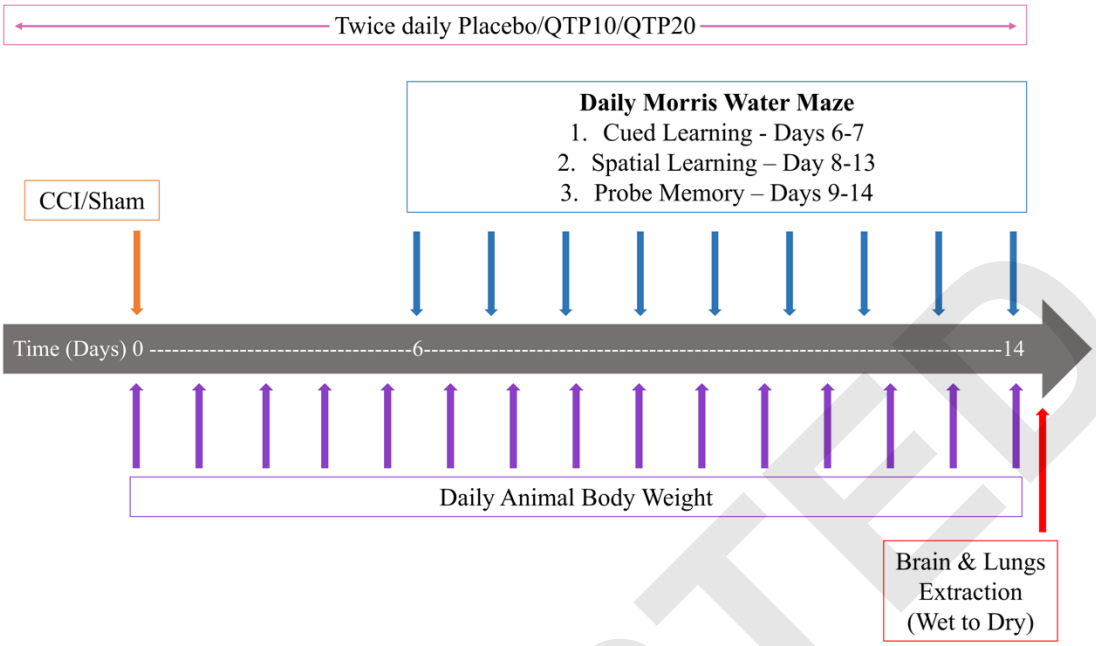


Figure 2

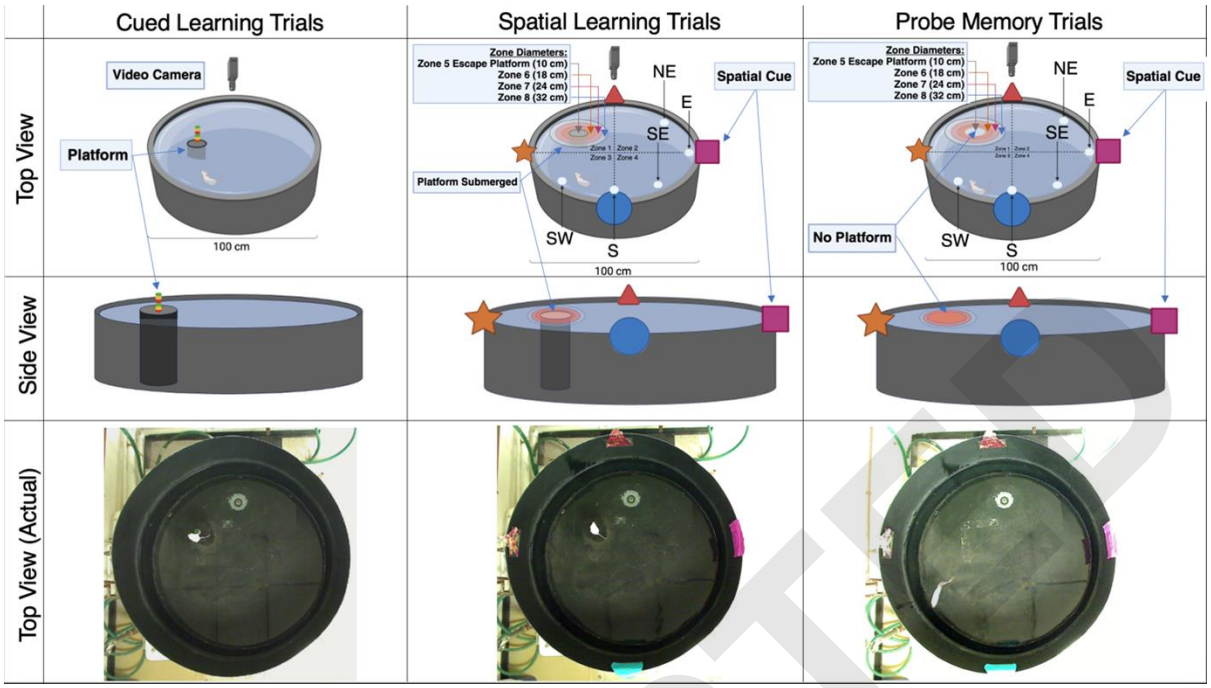
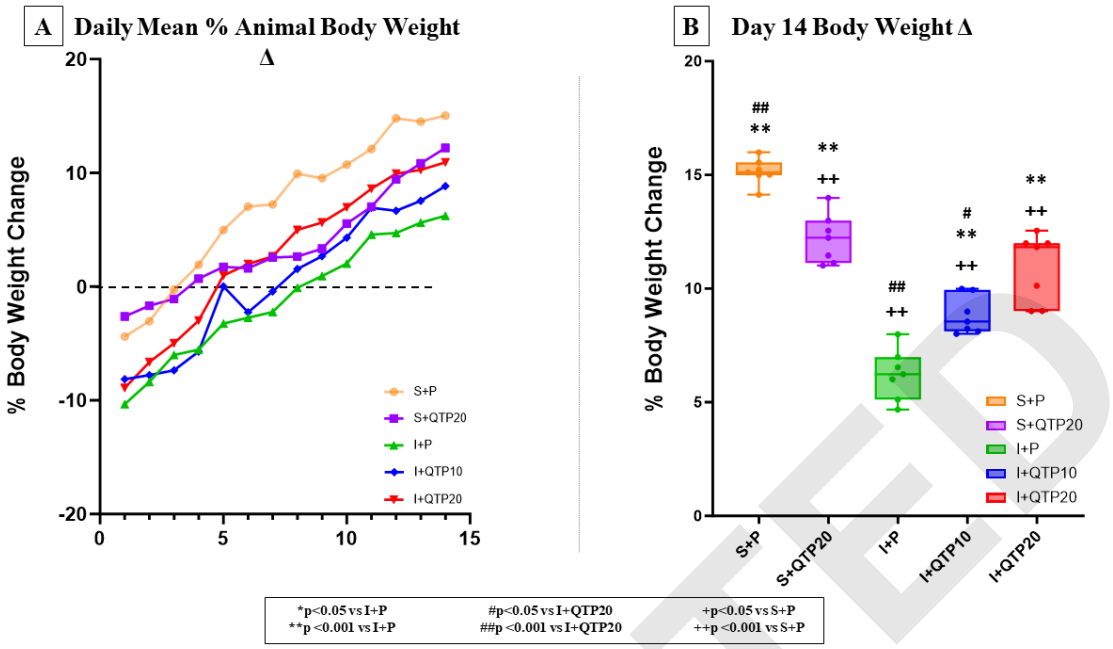


Figure 3



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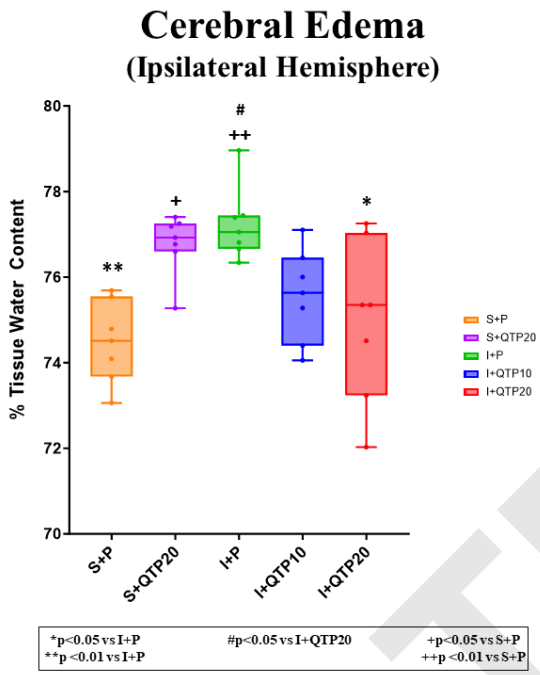

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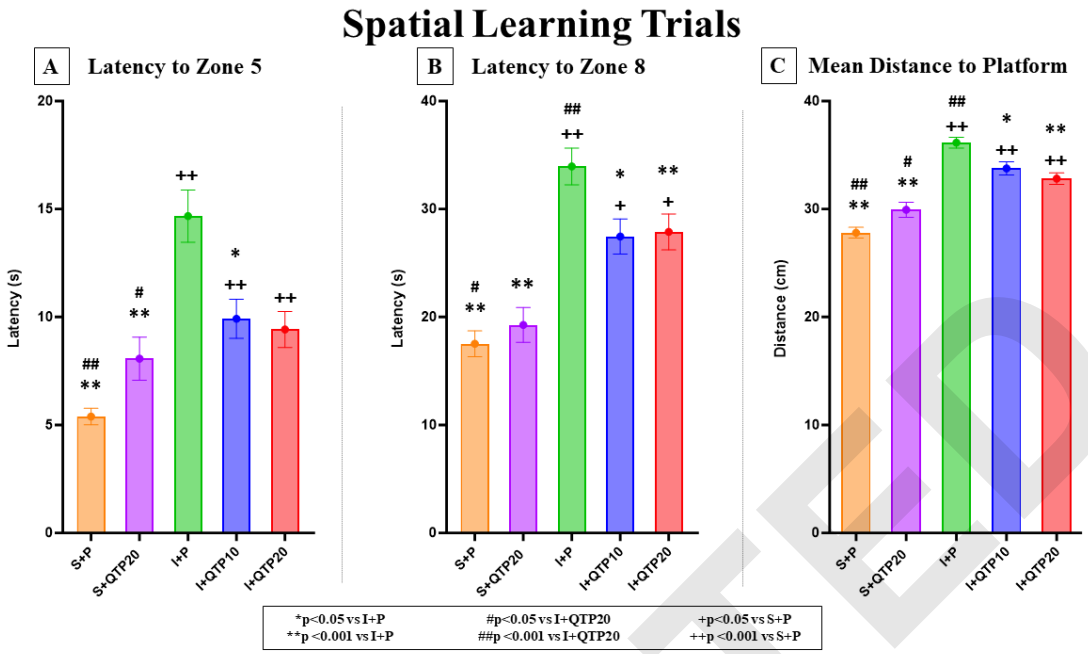
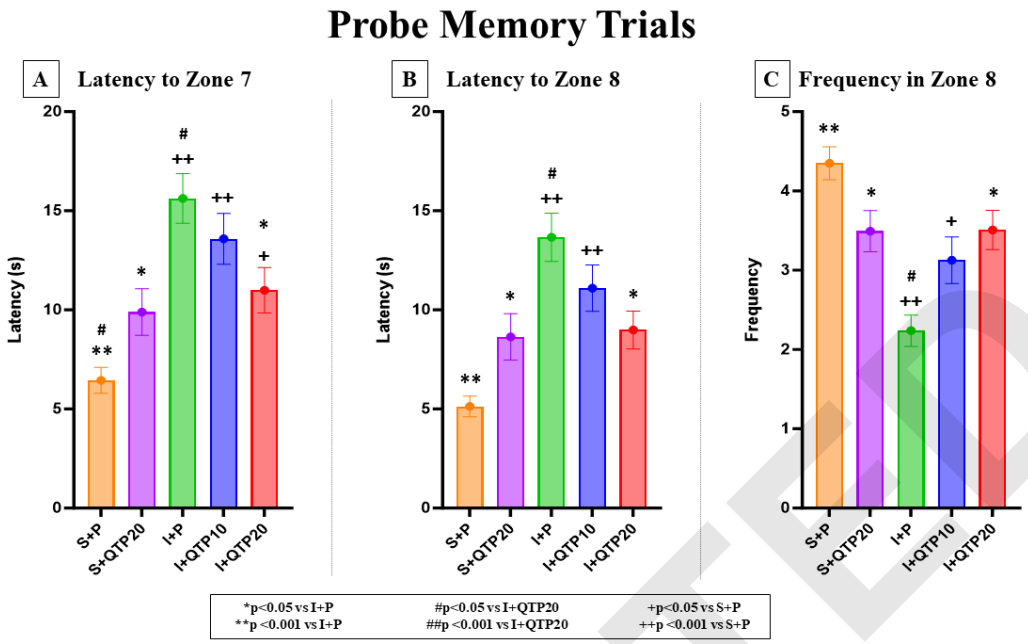


Figure 6



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Based on the ARRIVE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Essential 10			
Study design	#1a	Give details of the groups being compared,	2

		including control groups. If no control group has been used, the rationale should be stated.	
Study design	#1b	Give details of the experimental unit (e.g., a single animal, litter, or cage of animals).	2
Sample size	#2a	Specify the exact number of experimental units allocated to each group, and the total number in each experiment. Also indicate the total number of animals used.	3
Sample size	#2b	Explain how the sample size was decided. Provide details of any a priori sample size calculation, if done.	6
Inclusion and exclusion criteria	#3a	Describe any criteria used for including or excluding animals (or experimental units) during the experiment, and data points during the analysis. Specify if these criteria were established a priori. If no criteria were set, state this explicitly.	n/a
Inclusion and exclusion criteria	#3b	For each experimental group, report any animals, experimental units, or data points not included in the analysis and explain why. If there were no exclusions, state so.	n/a
Inclusion and exclusion criteria	#3c	For each analysis, report the exact value of n in each experimental group.	3
Randomisation	#4a	State whether randomisation was used to allocate experimental units to control and treatment groups. If done, provide the method used to generate the randomisation sequence.	3
Randomisation	#4b	Describe the strategy used to minimise potential confounders such as the order of treatments and measurements, or animal/cage location. If confounders were	3

		not controlled, state this explicitly.	
Blinding	#5	Describe who was aware of the group allocation at the different stages of the experiment (during the allocation, the conduct of the experiment, the outcome assessment, and the data analysis).	4
Outcome measures	#6a	Clearly define all outcome measures assessed (e.g., cell death, molecular markers, or behavioural changes).	4-6
Outcome measures	#6b	For hypothesis-testing studies, specify the primary outcome measure, i.e., the outcome measure that was used to determine the sample size.	4
Statistical methods	#7a	Provide details of the statistical methods used for each analysis, including software used.	6
Statistical methods	#7b	Describe any methods used to assess whether the data met the assumptions of the statistical approach, and what was done if the assumptions were not met.	6
Experimental animals	#8a	Provide species-appropriate details of the animals used, including species, strain and substrain, sex, age or developmental stage, and, if relevant, weight.	2
Experimental animals	#8b	Provide further relevant information on the provenance of animals, health/immune status, genetic modification status, genotype, and any previous procedures.	2
Experimental procedures	#9a	For each experimental group, including controls, describe the procedures in enough detail to allow others to replicate what was done, how it was done, and what was used.	3-4

Experimental procedures	#9b	Timing and frequency of procedures	3
Experimental procedures	#9c	Where procedures were carried out (including detail of any acclimatisation periods).	3-6
Experimental procedures	#9d	Rationale for procedures	3-6
Results	#10a	For each experiment conducted, including independent replications, report summary/descriptive statistics for each experimental group, with a measure of variability where applicable (e.g., mean and SD, or median and range).	
7-8 + figures			
Results	#10b	If applicable, for each experiment conducted, including independent replications, report the effect size with a confidence interval.	na
Recommended set			
Abstract	#11	Provide an accurate summary of the research objectives, animal species, strain and sex, key methods, principal findings, and study conclusions.	n/a
Background	#12a	Include sufficient scientific background to understand the rationale and context for the study, and explain the experimental approach.	1-2
Background	#12b	Explain how the animal species and model used address the scientific objectives and, where appropriate, the relevance to human biology.	1-2
Objectives	#13	Clearly describe the research question,	2

		research objectives and, where appropriate, specific hypotheses being tested.	
Ethical statement	#14	Provide the name of the ethical review committee or equivalent that has approved the use of animals in this study and any relevant licence or protocol numbers (if applicable). If ethical approval was not sought or granted, provide a justification.	na
Housing and husbandry	#15	Provide details of housing and husbandry conditions, including any environmental enrichment.	2
Animal care and monitoring	#16a	Describe any interventions or steps taken in the experimental protocols to reduce pain, suffering, and distress.	2-3
Animal care and monitoring	#16b	Report any expected or unexpected adverse events.	3
Animal care and monitoring	#16c	Describe the humane endpoints established for the study, the signs that were monitored, and the frequency of monitoring. If the study did not set humane endpoints, state this.	3-4
Interpretation/scientific implications	#17a	Interpret the results, taking into account the study objectives and hypotheses, current theory, and other relevant studies in the literature.	8-14
Interpretation/scientific implications	#17b	Comment on the study limitations, including potential sources of bias, limitations of the animal model, and imprecision associated with the results.	8-14
Generalisability/translation	#18	Comment on whether, and how, the findings of this study are likely to generalise to other species or experimental conditions, including any relevance to human biology (where appropriate).	8-14

Protocol registration	#19	Provide a statement indicating whether a protocol (including the research question, key design features, and analysis plan) was prepared before the study, and if and where this protocol was registered.	na
Data access	#20	Provide a statement describing if and where study data are available.	na
Declaration of interests	#21a	Declare any potential conflicts of interest, including financial and nonfinancial. If none exist, this should be stated.	na
Declaration of interests	#21b	List all funding sources (including grant identifier) and the role of the funder(s) in the design, analysis, and reporting of the study.	na

Notes:

10a: 7-8 + figures The ARRIVE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 25. January 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

The Journal of Trauma and Acute Care Surgery

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Manuscript Number (if known): TBD

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Time frame: Since the initial planning of the work			
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	Time frame: past 36 months		
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3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	

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8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	
14	Family Disclosure. Disclose any financial associations involving a spouse, partner, or children	☒ **None**	

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☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

The Journal of Trauma and Acute Care Surgery

CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 1/9/2024

Your Name: Advait Thaploo

Manuscript Title: DAILY QUETIAPINE AFTER SEVERE TBI IMPROVES LEARNING AND MEMORY UP TO TWO WEEKS AFTER INJURY

Manuscript Number (if known): TBD

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CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 7/31/2023

Your Name: Anastasia Georges

Manuscript Title: DELAYED TXA AFTER TBI IMPEDES LEARNING, MEMORY; EARLY TXA IS FAVORABLE BUT NOT IN SHAM ANIMALS

Manuscript Number (if known): TBD

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CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 7/31/2023

Your Name: Erin D. Anderson

Manuscript Title: DELAYED TXA AFTER TBI IMPEDES LEARNING, MEMORY; EARLY TXA IS FAVORABLE BUT NOT IN SHAM ANIMALS

Manuscript Number (if known): TBD

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CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 7/31/2023

Your Name: Kevin D. Browne

Manuscript Title: DELAYED TXA AFTER TBI IMPEDES LEARNING, MEMORY; EARLY TXA IS FAVORABLE BUT NOT IN SHAM ANIMALS

Manuscript Number (if known): TBD

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The Journal of Trauma and Acute Care Surgery

CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 1/9/2024

Your Name: Christina L. Jacovides

Manuscript Title: DAILY QUETIAPINE AFTER SEVERE TBI IMPROVES LEARNING AND MEMORY UP TO TWO WEEKS AFTER INJURY

Manuscript Number (if known): TBD

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CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 1/9/2024

Your Name: Patricia Santos Carlin

Manuscript Title: DAILY QUETIAPINE AFTER SEVERE TBI IMPROVES LEARNING AND MEMORY UP TO TWO WEEKS AFTER INJURY

Manuscript Number (if known): TBD

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The Journal of Trauma and Acute Care Surgery

CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 1/9/2024

Your Name: Lewis J Kaplan, MD

Manuscript Title: DAILY QUETIAPINE AFTER SEVERE TBI IMPROVES LEARNING AND MEMORY UP TO TWO WEEKS AFTER INJURY

Manuscript Number (if known): TBD

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7	Support for attending meetings and/or travel	☒ **None**	

UpToDate	Royalties paid to me

Medical Legal consulting	Monies paid to me

Society of Transplant Surgeons meeting	Travel expenses only

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	
14	Family Disclosure. Disclose any financial associations involving a spouse, partner, or children	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

The Journal of Trauma and Acute Care Surgery

CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 1/9/2024

Your Name: David F Meaney

Manuscript Title: DAILY QUETIAPINE AFTER SEVERE TBI IMPROVES LEARNING AND MEMORY UP TO TWO WEEKS AFTER INJURY

Manuscript Number (if known): TBD

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related or unrelated to the content of your manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

Participants of an accredited activity must disclose all personal **financial** and **non-financial relationships**, over the previous 36 months with an **ineligible company** (formerly defined as a commercial interest). **Financial relationships** are those relationships in which the individual benefits by receiving a salary, royalty, consulting fee, honoraria, ownership interest (e.g., stocks, stock options or other ownership interest), or other financial benefits, and may affect activity content relevant to products or services of an **ineligible company**, defined as an entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Research grants from **ineligible companies** are financial relationships that should be disclosed, even if the funds go to the researcher's institution and not to the individual researcher.

The author's relationships/activities/interests should be defined broadly and not only related to the manuscript in question. For example, if your manuscript pertains to the epidemiology of shock, you should declare all relationships with manufacturers of treatments used in shock, even if that form of treatment is not mentioned in the manuscript.

According to federal regulations approved by the US Senate, any amount equal to above $10 USD must be disclosed. Although disclosure of the total amount is not required on this form. Authors are encouraged to search the CMS Open Payments Database found at https://openpaymentsdata.cms.gov and report on the JTACS Conflict of Interest Disclosure form ALL COI, and any other conflicts related or unrelated to the manuscript being submitted to the Journal for the last 36 months/3 years.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

If the article is accepted, all author JTACS COI forms will be published as supplemental material with the article.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials,	☒ None	
			Click the tab key to add additional rows.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	medical writing, article processing charges, etc.) **No time limit for this item.**		
		Time frame: past 36 months	
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	
14	Family Disclosure. Disclose any financial associations involving a spouse, partner, or children	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

The Journal of Trauma and Acute Care Surgery

CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 1/9/2024

Your Name: Douglas H. Smith

Manuscript Title: DAILY QUETIAPINE AFTER SEVERE TBI IMPROVES LEARNING AND MEMORY UP TO TWO WEEKS AFTER INJURY

Manuscript Number (if known): TBD

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related or unrelated to the content of your manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials,	☐ None	
		National Institutes of Health grant funding	University of Pennsylvania
		Department of Defense grant funding	University of Pennsylvania

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	medical writing, article processing charges, etc.) **No time limit for this item.**	Uniformed Services University of Health Services Grant funding	University of Pennsylvania
		Department of Army USAMRAA	University of Pennsylvania
		Allen Foundation grant funding	University of Pennsylvania
	Time frame: past 36 months		
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None** Listed above	
3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None** University of Pittsburgh speaker	Paid to Douglas Smith
		University of Michigan speaker	Paid to Douglas Smith
		LEIDOS review committee	Paid to Douglas Smith
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
8	Patents planned, issued or pending	☐ **None**	
		US 6264944 Mechanically Elongated Neuronal Cells 2001	No revenue generated or royalties to date.
		US 6365153 Mechanically elongated neuronal cells and methods for producing and using these cells 2002	
		US 7,429,267 Device and method using integrated neuronal cells and an electronic device 2008	
		US 7,972,367 Device and method using integrated neuronal cells and an electronic device 2011	
		US 8,400,636 Blast injury dosimeter 2013	
		US 8790666 Nerve construct containing living stretch-grown nervous tissue 2014	
		US 9,895,399 Repair of peripheral nerve injury 2015	
		CA 2,380,943 Mechanically Elongated Neuronal Cells and Methods for Producing These Cells 2010	
		Japan 4679780 Mechanically Elongated Neural Cells and Methods for Producing and Using these Cells 2011	
		EU 1225906 Mechanically Elongated Neural Cells and Methods for Producing and Using these Cells 2008	
		Australia – 766096 Mechanically Elongated Neuronal Cells and Methods for Producing These Cells 2004	
		Denmark - 1225906 Mechanically Elongated Neural Cells and Methods for Producing and Using these Cells 2008	
		US 10525085 Repair of peripheral nerve injury 2020	
		US – 17358851 Implantable Living Electrodes and Methods for use Thereof 2021	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☐ **None**	
		Mind Your Brain Foundation	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☐ **None**	
		Axonova Medical LLC	Co-Founder; no profits or income to date.
14	Family Disclosure. Disclose any financial associations involving a spouse, partner, or children	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

The Journal of Trauma and Acute Care Surgery

CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

Date: 7/31/2023

Your Name: Jose L. Pascual L.

Manuscript Title: DELAYED TXA AFTER TBI IMPEDES LEARNING, MEMORY; EARLY TXA IS FAVORABLE BUT NOT IN SHAM ANIMALS

Manuscript Number (if known): TBD

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related or unrelated to the content of your manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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			Click the tab key to add additional rows.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	medical writing, article processing charges, etc.) **No time limit for this item.**		
		Time frame: past 36 months	
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
		Multiple presentations for SCCM Executive	No payments
6	Payment for expert testimony	☐ **None**	
		Multiple firms for plaintiff and defendant Council	As per standard fee schedule U Penn
7	Support for attending meetings and/or travel	☐ **None**	
		SCCM, AAST, ACS	To cover travel, lodging and registration at conference

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☐ **None**	
		SCCM Secretary	
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	
14	Family Disclosure. Disclose any financial associations involving a spouse, partner, or children	☒ **None**	

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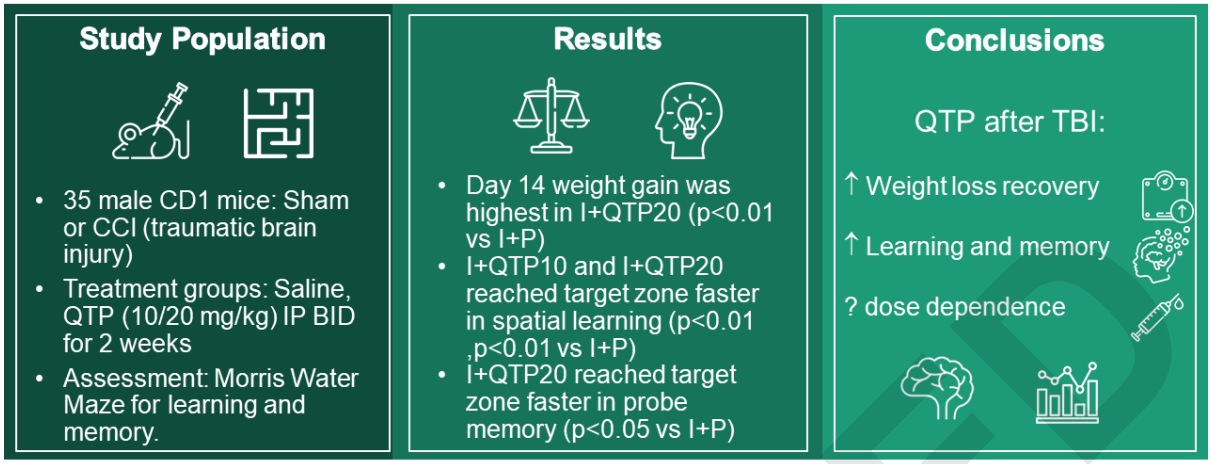
DAILY QUETIAPINE AFTER SEVERE TBI IMPROVES LEARNING AND MEMORY



Bele P et al. *Journal of Trauma and Acute Care Surgery*.
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