**Table e-1: Table with search terms**

The search term for pupillometer (pupillometry OR pupillography OR pupillometer OR automated pupillary OR apparative pupillary) was used in combination with the search terms listed below

| **Topic** | **Keywords identified** | **Search terms used** |
| --- | --- | --- |
| Anatomy | Cornea | cornea, corneopathy |
|  | Iris | iris |
|  | M. sphincter pupillae | musculus sphincter pupillae, pupillary sphincter, iris sphincter muscle, pupillary constrictor  |
|  | M. dilatator pupillae | Musculus dilatator pupillae, pupillary dilator, iris dilator muscle, pupil dilator muscle  |
|  | Vitreous body | vitreous, vitreus |
|  | Retina | retina, retinopathy, Rete |
|  | Nervus opticus | nervus opticus, optic nerve |
|  | Nervus oculomotorius | nervus oculomotorius, oculomotor nerve  |
|  | Occipital cortex | occipital cortex, occipital lobe, lobus occipitalis |
| Drugs | Opioids | opioid |
|  |  | Morphine | morphine, pethidine, meperidine, hydromorphone |
|  |  | Fentanyl (Sufentanyl, Ramifentanyl) | fentanyl, remifentanil, sufentanil |
|  | Neuromuscular blocking drugs | Neuromuscular blocking |
|  |  | Different neuromuscular blocking drugs | Rapacuronium, Raplon, Mivacurium, Mivacron, Atracurium, Tracrium, Doxacurium, Nuromax, Cisatracurium, Nimbex, Vecuronium, Norcuron, Rocuronium, Zemuron, Pancuronium, Pavulon, Tubocurarine, Jexin, gallamine, Flaxedil, Pipecuronium |
|  | Benzodiazepines | benzodiazepine |
|  |  | Different diazepines | Alprazolam, Bromazepam, Bromazolam, Camazepam, Clonazepam, Clonazolam, Diazepam, Lorazepam, Lormetazepam, Midazolam, Oxazepam, Temazepam |
|  | Vasoactive drugs | vasopressor, pressor, antihypotensive, sympathomimetic |
|  |  | Different vasopressors | epinephrine, noradrenaline, phenylephrine, dobutamine, dopamine, ephedrine, midodrine, amezinium |
|  | Sedatives |  |
|  |  | Propofol | Propofol, Propanol, Propranolol |
|  |  | Ketamine | Ketamine, Ketalar |
|  | Antiepileptic drugs | anticonvulsant, antiepileptic, antiseizure |
|  |  | Classes & different drugs | Aldehyde, Barbiturate, Benzodiazepine, Bromide, Carbamate, Carboxamide, GABA, Hydantoin, Oxazolidinedione, Propionate, Pyrimidinedione, Pyrrolidine, Succinimide, Sulfonamide, Triazine, Valproylamide, paraldehyde, phenobarbital, methylphenobarbital, Barbexaclone, Clobazam, Clonazepam, Clorazepate, Diazepam, Midazolam, Lorazepam, Carbamazepine, Oxcarbazepine, Eslicarbazepine, valproate, Vigabatrin, Progabide, Tiagabine, Topiramate, Gabapentin, Pregabalin, Ethotoin, Phenytoin, Mephenytoin, Fosphenytoin, Ethosuximide, Phensuximide, Paramethadione, Trimethadione, Ethadione, Beclamide, Primidone, Brivaracetam, Etiracetam, Levetiracetam, Seletracetam, Mesuximide, Acetazolamide, Sultiame, Methazolamide, Zonisamide, Lamotrigine, Valpromide, Valnoctamide, Pheneturide, Phenacemide |
| ICU-specific | cardiac arrest | cardiac arrest, heart arrest, CPR, resuscitation |
|  | hypoxia  | hypoxia, hypoxemia, hypoxaemia, hypoxic, ischaemic, ischemic, stroke |
|  | encephalopathy | encephalopathy, encephalitis |
|  | critical care | critical care, intensive care, neurocritical, critically |
|  | intracranial | intracranial |
|  | monitor | monitor, monitoring |
|  | coma | coma |
|  | delirium | delirium, confusion |
|  | meningitis | meningitis |
|  | intracranial injury | acute, traumatic, brain, head, intracranial, injury, lesion |
|  | intracranial haemorrhage | bleed, hemorrhage, haemorrhage, bleeding, hemorrhaging, haemorrhaging, subarachnoid, arachnoid, subdural, dural, epidural |
|  | uncal herniation | uncal, herniation, cranial, pressure |
|  | acidemia | acidosis, acidemia, acidaemia |
|  | hypothermia | hypothermia |

Examples of searches performed:

* Cornea: (pupillometry OR pupillography OR pupillometer OR automated pupillary OR apparative pupillary) AND (cornea OR corneopathy)
* Uncal herniation: (pupillometry OR pupillography OR pupillometer OR automated pupillary OR apparative pupillary) AND (uncal OR herniation OR cranial OR pressure)

**Table e-2: Overview of possible neurological confounders with their influence on pupillometry**

| **Potential confounder** | **Number of identified studies** | **Total N of patientsa** | **Study types** | **Effect on static pupil parametersb** | **Effect on dynamic pupil parametersc** | **Type of pupillometerd** |
| --- | --- | --- | --- | --- | --- | --- |
| Increased cranial pressure | 1-10 | 649 | * Prospective cohort (N=76, mean 55.4, SD 16.7)
* Prospective cohort (N=76, mean 55.4, SD 16.7)
* Prospective observational (N=72, mean 57.4, SD 16)
* Prospective observational (N=40, RNG 19-79)
* Observational cohort (N=54, mean 54 SD 21)
* Case control (N=41, mean 32, RNG 22-49)
* Exploratory study (N=18, mean 57.7, SE 3.0)
* Retrospective analysis of a database (N=134, mean 65.1 SD 15.2)
* Case-series (N=3, mean 29, SD 5.5)
* NR (N=134, mean 46, RNG 18-87)
 | * Yes: 3x
* Weak predictor, low level of significance: 1x
* No (online supp table): 1x
* No: 1x
* Unclear: 1x
* NR: 3x
 | * Yes: 9x
* Weak (statistically insignificant): 1x
 | * NPi-100: 5x
* Neuroptics NOS: 1x
* NPi-200: 4x
 |
| Traumatic brain injury | 7, 11, 12 | 126 | * Observational cohort (N=54, mean 54 SD 21)
* Age-matched controls (N=40, age 31.2 SD 7.4, RNG 20-43, case N=20, control N=20)
* Case-control (N=32, case N=17, mean 31 SD 6, control N=15 mean 26 SD 5)
 | * Yes: 1x
* No: 1x
* NR: 1x
 | * Yes: 2x
* Yes (6-month GOS 4-5 vs 1-3)
 | * PLR-200: 2x
* NPi-200: 1x
 |
| Ischemic brain damage | 13-15 | 77 | * Case-control (total N=75, case N=50, mean 71.8, SD 10.8)
* Case report (N=1, age=71)
* Case report (N=1, age=78)
 | * NR: 1x
* No (Stroke affecting insular cortex and prefrontal eye field): 1x
* No (Brain edema after brain infarction treated with TTM for constriction velocity): 1x
* Yes (Brain edema after brain infarction treated with TTM for size): 1x
 | * Yes: 2x
* No (subtle changes due to autonomic dysfunction yes): 1x
 | * NPi-200: 2x
* NPi-100: 1x
 |
| Neurodegenerative disorders (parkinson, Alzheimer (incl preclinical Alzheimer)) | 16, 17 | 159 | * Case-control (Total N=30, Case N=16, mean 54 SD 10, control N=14 mean 63 SD 7)
* Case-control (Total N=129, case N=14, mean 77.4 SD 5.4, control N=115, mean 72.9, SD 5.3)
 | * Yes: 2x
 | * No: 1x
* Yes: 1x
 | * Neurolight: 1x
* VIP-200: 1x
 |
| Third cranial nerve alteration | 18, 19 | 172 | * Retrospective observational case series (Total N=171, Ischemic N=60, mean 67.3 SD 9.3, Inflammatory N=21, mean 64.5 SD 9.6, Compressive N=30 mean 64.9 SD 9.7)
* Case report (N=1, age=53)
 | * Yes: 3x
* Unclear: 1x
 | * Yes: 2x
* Yes, low sensitivity: 1x
* Unclear: 1x
 | * PLR-200: 1x
* NPi-200: 1x
 |
|  |  |  |  |  |  |  |
| Aneurysmal subarachnoid hemorrhage | 6 | 18 | * Exploratory study (N=18, mean 57.7, SE 3.0)
 | * No (online supp table): 1x
 | * Highly likely: 1x
 | * NPi-200: 1x
 |
| Adequate seizure during electroconvulsive therapy | 20 | 13 | * Observational, non-randomized, not controlled (Total N=13, median 64, IQR 54-68)
 | * Yes
 | * NR
 | * NPi-100
 |
| Encephalopathy | 21  | 60 | * Prospective study (N=60, mean 66, IQR 56 – 79)
 | * Yes
 | * Yes
 | * Aligiscan
 |
| Hypoxemia and hypercarbia | 22 | 10 | * Volunteer (Total N=10, mean 29 SD 3)
 | * Yes
 | * No
 | * Neuroptics NOS
 |
| Others | * 23 Cluster headache
* 24 Parasympathic activation (hypotension in spinal anesthesia)
 | 260 | * Prospective, single center (Total N=200, Hypotension N=141 mean 31 SD 5)
* Case-control (Ntotal=60, case N=30, mean 50.2, SD 13.6)
 | * Yes: 2x
 | * Yes: 2x
 | * PLR-200
* Neurolight
 |

Because a single study can report on multiple outcomes, not all totals will add up to 100%

Abbreviations: NR = Not reported; SD = standard deviation; SE = standard error, SEM = standard error of the mean, RNG = range, IQR = interquantile/interquartile range, 95%CI = 95% condifence interval, NOS = not otherwise specified, ICU = intensive care unit, SSNRI = selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI)

a In case-control studies, only the cases are counted.

b Parameters considered as static include a positive finding one or more of the following parameters: pupil size, pupil minimum diameter, pupil maximum diameter, changes in pupillary diameter from baseline

c Parameters considered as dynamic include a positive finding one or more of the following parameters: pupil constriction velocity, pupil dilatation velocity, pupil latency, NPi

d Type of pupillometers:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Abbreviation** | **Name** | **Company** | **City** | **State** | **Country** |
| NeurOptics NOS | NeurOptics pupillometer type not specified, but monocular as specified by research methods | NeurOptics | Irvine | California | United States of America |
| NPi-100 | NPi-100 | NeurOptics | Irvine | California | United States of America |
| NPi-200 | NPi-200 | NeurOptics | Irvine | California | United States of America |
| VIP-200 | VIP-200 | NeurOptics | Irvine | California | United States of America |
| PLR-200 | PLR-200 | NeurOptics | Irvine | California | United States of America |
| ForSite | ForSite digital pupillometer | NeurOptics | Irvine | California | United States of America |
| Neurolight | Neurolight | IDMed | Marseille |  | France |
| Neurolight v1.2 | Neurolight version 1.2 | IDMed | Marseille |  | France |
| IDMed | IDMed pupillometer type not otherwise specified, but monocular as specified by research methods | IDMed | Marseille |  | France |
| Algiscan | NeuroLight Algiscan | IDMed | Marseille |  | France |
| Applied sciences |  |  |  |  |  |

**Table e-3: Overview of possible ICU-specific and anesthesiology-specific confounders with their influence on pupillometry**

| **Potential confounder** | **Number of identified studies** | **Total N of patientsa** | **Study types** | **Effect on static pupil parametersb** | **Effect on dynamic pupil parametersc** | **Type of pupillometerd** |
| --- | --- | --- | --- | --- | --- | --- |
| Depth of sedation  | 25 | 31 | * Monocentric, observational study (N=31, mean 57 SD 14)
 | * Yes
 | * Yes
 | * Neurolight
 |
| Pain | 26-39 | 1209 | * Randomized proof of concept (N=76, mean 28 SD 6)
* Single center interventional cohort (Total N=38, mean 46.53 SD 13.27 RNG 24-74)
* Single-centre interventional cohort (Total N=34, mean 45, SD 14)
* Prospective observational (Total N=24, median 49, IQR 34 to 59)
* Prospective observational (Total N=100, median 58 95%CI 52 to 62)
* Prospective observational (Total N=130, First stage N=26 (mean 32 SD 5 RNG 23-41) Second stage N=104 (mean 30, SD 5 RNG 18-41))
* Prospective, observational, cohort (Total N=103, mean 62.3 SD 14.9)
* Prospective observational (Total N=40, brain injured N=20 median 48 IQR 39–60. Non-brain injured N=20, median 52 IQR 43–60.
* Prospective (N=34, mean 56 SD 19)
* Prospective observational (N=102, median 72 IQR 60-77
* Cross-sectional cohort (Total N=145, mean 50 SD 17)
* Preliminary (Total N=37, median=54, RNG 39-63)
* Case report (N=1, age 41)
* NR (N=345, mean 50, SD 17, RNG 18 – 91)
 | * Yes: 11x
* Yes in a brain injured patient: 1x
* No: 2x
 | * NR: 13x
* Yes: 1x
 | * Neurolight: 5x
* Neurolight v1.2: 2x
* Algiscan: 6x
* IDMed: 1x
 |
| Time to extubation after surgery | 38 | 102 | * Prospective observational (N=102, median 72 IQR 60-77
 | * Yes
 | * NR
 | * AlgiScan
 |
| Delirium in the post-anesthesia care unit | 40 | 47 | * Prospective observational (Total N=47, total group information NR)
 | * Yes at 60 min
 | * Yes at 60 min
 | * PLR-200
 |
| Hyperthermia | 41 | 31 | * NR (Total N=31, mean 30 SD 6)
 | * No
 | * No
 | * Applied Sciences
 |
| Targeted temperature measurement | 15 | 1 | * Case report (N=1, age=78)
 | * No
 | * No
 | * NPi-200
 |

Because a single study can report on multiple outcomes, not all totals will add up to 100%

Abbreviations: NR = Not reported; SD = standard deviation; SE = standard error, SEM = standard error of the mean, RNG = range, IQR = interquantile/interquartile range, 95%CI = 95% condifence interval, NOS = not otherwise specified, ICU = intensive care unit, SSNRI = selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI)

a In case-control studies, only the cases are counted.

b Parameters considered as static include a positive finding one or more of the following parameters: pupil size, pupil minimum diameter, pupil maximum diameter, changes in pupillary diameter from baseline

c Parameters considered as dynamic include a positive finding one or more of the following parameters: pupil constriction velocity, pupil dilatation velocity, pupil latency, NPi

d Type of pupillometers:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Abbreviation** | **Name** | **Company** | **City** | **State** | **Country** |
| NeurOptics NOS | NeurOptics pupillometer type not specified, but monocular as specified by research methods | NeurOptics | Irvine | California | United States of America |
| NPi-100 | NPi-100 | NeurOptics | Irvine | California | United States of America |
| NPi-200 | NPi-200 | NeurOptics | Irvine | California | United States of America |
| VIP-200 | VIP-200 | NeurOptics | Irvine | California | United States of America |
| PLR-200 | PLR-200 | NeurOptics | Irvine | California | United States of America |
| ForSite | ForSite digital pupillometer | NeurOptics | Irvine | California | United States of America |
| Neurolight | Neurolight | IDMed | Marseille |  | France |
| Neurolight v1.2 | Neurolight version 1.2 | IDMed | Marseille |  | France |
| IDMed | IDMed pupillometer type not otherwise specified, but monocular as specified by research methods | IDMed | Marseille |  | France |
| Algiscan | NeuroLight Algiscan | IDMed | Marseille |  | France |
| Applied sciences |  |  |  |  |  |

**Table e-4: Overview of possible medication/drugs confounders with their influence on pupillometry**

| **Potential confounder** | **Subtopic** | **References** | **Total N of patientsa** | **Study types** | **Effect on static pupil parametersb** | **Effect on dynamic pupil parametersc** | **Type of pupillometerd** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Drugs with known CNS effect | L-DOPA | 16 | 30 | * Case-control (Total N=30, Case N=16, mean 54 SD 10, control N=14 mean 63 SD 7)
 | * Yes
 | * No
 | * Neurolight
 |
| Barbiturate coma (exaggerated ciliospinal reflex) | 42 | 1 | * Case report (N=1, age 76)
 | * Yes
 | * Yes
 | * Neuroptics NOS
 |
| Opioids | 22, 30, 33, 43-49 | 269 | * Double-blinded, randomized, five-way, placebo-controlled, cross-over (N=12, RNG 22-32)
* Two treatment arms of a randomized, double blind, placebo-controlled four-way crossover (Total N=15, mean 25.5, RNG 20-56)
* Phase 1, open, randomized, two-way, cross-over pharmacokinetic and pharmacodynamic (N=12 mean 23.8 95%CI 22.6-25)
* Randomized, double-blind, placebo-controlled, crossover (N=10, mean 31.2 SEM 2.27)
* Double-blind, within-subject, placebo-controlled (N=9, mean 24 SEM 1)
* Double-blind, within-subject, placebo-controlled (N=10, age mean 37 SD 8)
* Single-center interventional cohort (Total N=34, mean 45, SD 14)
* Cross-sectional cohort (Total N=145, mean 50 SD 17)
* Exploratory, descriptive, open pharmokinetic-pharmodynamic (Total N=12, mean 23.0 (RNG 19-26)
* Volunteer (Total N=10, mean 29 SD 3)
 | Yes:* Remifentanil
* Morphine
* Morphine
* Tapentadol 25mg
* Tapentadol 50mg
* Tapentadol 75mg
* Tramadol 100mg
* Tramadol 150mg
* Hydromorphone 2mg
* Hydromorphone 4mg
* Hydromorphone 6mg
* Hydromorphone 16mg
* Tramadol 350mg
* Buprenorphine
* Buprenorphine/Naloxone
* Remifentanil 95%CI
* Remifentanil 95% CI
* Remifentanil

No:* Tramadol 50mg
* Tramadol 87.5mg
* Tramadol 175mg
 | NR* Remifentanil
* Morphine
* Morphine
* Tapentadol
* Tramadol
* Tramadol
* Hydromorphone
* Tramadol
* Buprenorphine
* Buprenorphine/Naloxone
* Remifentanil
* Remifentanil

No:* Remifentanil
 | * Algiscan
* Neurolight
* PLR-200
* PLR-100
* VIP-200
* Neuroptics NOS:2x
 |
| Long-term (4 week) use of high-dose opioids (equivalent to at least 60mg morphine) | 50 | 83 | * Case control (Total N=83, patient N=63 median 61, IQR 53 - 69, control N=20, median 55 IQR 34 – 61)
 | * No
 | * No
 | * Algiscan
 |
| Residual effect intraoperative opioids | 32 | 103 | * Prospective, observational, cohort (Total N=103, mean 62.3 SD 14.9)
 | * Yes
 | * NR
 | * Neurolight
 |
| Naloxone for blocking miotic effects | 44, 48, 49 | 34 | * Double-blind, within-subject, placebo-controlled (N=10, mean 37 SD 8)
* Phase 1, open, randomized, two-way, cross-over pharmacokinetic and pharmacodynamic (N=12 mean 23.8 95%CI 22.6-25)
* Exploratory, descriptive, open pharmokinetic-pharmodynamic (Total N=12, mean 23.0 (RNG 19-26)
 | * Yes Hydromorphone: 1x
* Yes Tramadol: 1x
* Yes Remifentanyl: 2x yes
* Yes (95%CI): 1x
 | * NR: 3x
 | * VIP-200: 2x
* PLR-200: 1x
 |
| Autonomic drugs (MDMA, Ecstacy) | 51 | 80 | * Pooled analysis of five double-blind, double-dummy, placebo-controlled, randomized, crossover studies (Total N=80, mean 25 SD 5)
 | * Yes
 | * Yes
 | * PLR-200
 |
| GABA-receptor agonist (Propofol) | 52 | 19 | * Cross-sectional (Total N=19, median 58 IQR 47-67)
 | * Yes
 | * Yes (latency only between baseline and induction)
 | * NPi-100
 |
| NMDA-antagonist (Ketamine) | 53 | 32 | * Randomized study, (Total N=32, Ketamine N=8, age 59.6 SD 10)
 | * Yes for percent constriction: 1x
* No for pupil size: 1x
 | * Yes (latency)
 | * ForSite
 |
| NMDA-antagonist (Nitrous oxide) | 41, 53 | 63 | * Randomized study, (Total N=32, Nitrous oxide N=8, age 59.7 SD 17)
* NR (Total N=31, mean 26 SD 5)
 | * Yes: 1x (author note: not clinically important)
* Yes for percent constriction: 1x
* No for pupil size: 1x
 | * Yes: 1x (author note: not clinically important)
* Yes latency: 1x
 | * Applied Sciences: 1x
* ForSite: 1x
 |
| Norepinephrine transporter inhibitor (Reboxetine) | 51 | 80 | * Pooled analysis of five double-blind, double-dummy, placebo-controlled, randomized, crossover studies (Total N=80, mean 25 SD 5)
 | * Yes
 | * No
 | * PLR-200
 |
| SSNRI (Duloxetine) | 51 | 80 | * Pooled analysis of five double-blind, double-dummy, placebo-controlled, randomized, crossover studies (Total N=80, mean 25 SD 5)
 | * Yes
 | * No
 | * PLR-200
 |
| SSRI (Paroxetine & Escitalopram) | 45, 54  | 25 | * Double-blinded, randomized, five-way, placebo-controlled, cross-over (N=12, RNG 22-32)
* Randomized, double-blind, placebo-controlled, two-phase, crossover, phenotype panel trial (N=13, extensive metabolizer N=8 median 25 RNG 21-32, poor metabolizer N=5 median 24, RNG 21-27)
 | * Yes: 1x
* No: 1x
 | * NR: 2x
 | * PLR-100: 1x
* NeurOptics PLR NOS: 1x
 |
| Dopamine agonists (Aripiprazole) | 55 | 32 | * Phase I, single oral dose, randomized, crossover, two periods, two sequences, open-label, single-centre study, with blind determination of the plasma concentrations (N=32, men age 25.6 ± 7.0 years and women age 31.0 ± 10.7 years, p = 0.06)
 | * Yes
 | * Yes
 | * PLR-200
 |
| Seretonine receptor agonist (Aripiprazole) | 55 | 32 | * Phase I, single oral dose, randomized, crossover, two periods, two sequences, open-label, single-centre study, with blind determination of the plasma concentrations (N=32, men age 25.6 ± 7.0 years and women age 31.0 ± 10.7 years, p = 0.06)
 | * Yes
 | * Yes
 | * PLR-200
 |
| α2-adregenic receptor agonist (Clonidine) | 51 | 80 | * Pooled analysis of five double-blind, double-dummy, placebo-controlled, randomized, crossover studies (Total N=80, mean 25 SD 5)
 | * Yes
 | * No
 | * PLR-200
 |
| α1β-adregenic receptor antagonist (Carvedilol) | 51 | 80 | * Pooled analysis of five double-blind, double-dummy, placebo-controlled, randomized, crossover studies (Total N=80, mean 25 SD 5)
 | * No
 | * No
 | * PLR-200
 |
| Inhalative anesthetics (isoflurane, enflurane) | 41 | 31 | * NR (Total N=31, isoflurane only NR, enflurane only NR)
 | * Yes Isoflurane 0.8%: 1x
* Yes Isoflurane 1.2%: 1x
* Yes Enflurane 1.7%: 1x
 | * Yes Isoflurane 0.8%: 1x
* Yes Isoflurane 1.2%: 1x
* Yes Enflurane 1.7%: 1x
 | * Applied Sciences: 1x
 |
| Anesthethics (sevoflurane–remifentanil, sevoflurane, desflurane–remifentanil, propofol–remifentanil | 56 | 35 | * Observational, non-randomized, non-controlled (N=35, age NR)
 | Sevoflurane-remifentanil: * Pupil size ratio Yes: 1x
* Maximum: no

Sevoflurane: * Pupil size ratio Yes: 1x
* Maximum: no

Desflurane-remifentanyl: * Pupil size ratio Yes: 1x
* Maximum: no

Propofol-remifentanyl: * Pupil size ratio Yes: 1x
* Maximum: no
 | Sevoflurane-remifentanil: * NPi: Yes 1x
* Latency: no

Sevoflurane: * NPi: Yes 1x
* Latency: no

Desflurane-remifentanyl: * NPi: Yes 1x
* Latency: no

Propofol-remifentanyl: * NPi: Yes 1x
* Latency: no
 | * NPi-100
 |
| Drugs without CNS effect | α1-adrenoreceptor antagonists (Doxazosin, Tamsulosin, Alfuzosin, Terazosin) | 51, 57 | 145 | * Pooled analysis of five double-blind, double-dummy, placebo-controlled, randomized, crossover studies (Total N=80, mean 25 SD 5)
* Prospective case control (Total N=65, Tamsulozin N=15, Alfuzosin N=22)
 | * No: 1x
* Yes : 1x
 | * No: 1x
* Yes: 1x
 | * PLR-200: 1x
* ForSite: 1x
 |

Because a single study can report on multiple outcomes, not all totals will add up to 100%

Abbreviations: NR = Not reported; SD = standard deviation; SE = standard error, SEM = standard error of the mean, RNG = range, IQR = interquantile/interquartile range, 95%CI = 95% condifence interval, NOS = not otherwise specified, ICU = intensive care unit, SSNRI = selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI)

a In case-control studies, only the cases are counted.

b Parameters considered as static include a positive finding one or more of the following parameters: pupil size, pupil minimum diameter, pupil maximum diameter, changes in pupillary diameter from baseline

c Parameters considered as dynamic include a positive finding one or more of the following parameters: pupil constriction velocity, pupil dilatation velocity, pupil latency, NPi

d Type of pupillometers:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Abbreviation** | **Name** | **Company** | **City** | **State** | **Country** |
| NeurOptics NOS | NeurOptics pupillometer type not specified, but monocular as specified by research methods | NeurOptics | Irvine | California | United States of America |
| NPi-100 | NPi-100 | NeurOptics | Irvine | California | United States of America |
| NPi-200 | NPi-200 | NeurOptics | Irvine | California | United States of America |
| VIP-200 | VIP-200 | NeurOptics | Irvine | California | United States of America |
| PLR-200 | PLR-200 | NeurOptics | Irvine | California | United States of America |
| ForSite | ForSite digital pupillometer | NeurOptics | Irvine | California | United States of America |
| Neurolight | Neurolight | IDMed | Marseille |  | France |
| Neurolight v1.2 | Neurolight version 1.2 | IDMed | Marseille |  | France |
| IDMed | IDMed pupillometer type not otherwise specified, but monocular as specified by research methods | IDMed | Marseille |  | France |
| Algiscan | NeuroLight Algiscan | IDMed | Marseille |  | France |
| Applied sciences |  |  |  |  |  |

**Table e-5: Overview of other possible confounders with their influence on pupillometry**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Potential confounder** | **Number of identified studies** | **Total N of patientsa** | **Study types** | **Effect on static pupil parametersb** | **Effect on dynamic pupil parametersc** | **Type of pupillometerd** |
| Circadian rhythm | 6 | 18 | * Exploratory study (N=18, mean 57.7, SE 3.0)
 | * NR
 | * Yes
 | * NPi-200
 |
| Sex | 58 | 263 | * Cohort (Total N=263, RNG 18-79)
 | * No
 | * NR
 | * PLR-200
 |
| Hypobaric hypoxia (Altitude sickness) | 59 | 17 | * Prospective observational (N=17, N=15 for 4800m, RNG 21–68)
 | * Yes (max only)
 | * Yes
 | * ForSite
 |

Because a single study can report on multiple outcomes, not all totals will add up to 100%

Abbreviations:

NR = Not reported; SD = standard deviation; SE = standard error, SEM = standard error of the mean, RNG = range, IQR = interquantile/interquartile range, 95%CI = 95% condifence interval, NOS = not otherwise specified, ICU = intensive care unit, SSNRI = selective serotonin and norepinephrine reuptake inhibitor antidepressant (SSNRI)

a In case-control studies, only the cases are counted.

b Parameters considered as static include a positive finding one or more of the following parameters: pupil size, pupil minimum diameter, pupil maximum diameter, changes in pupillary diameter from baseline

c Parameters considered as dynamic include a positive finding one or more of the following parameters: pupil constriction velocity, pupil dilatation velocity, pupil latency, NPi

d Type of pupillometers:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Abbreviation** | **Name** | **Company** | **City** | **State** | **Country** |
| NeurOptics NOS | NeurOptics pupillometer type not specified, but monocular as specified by research methods | NeurOptics | Irvine | California | United States of America |
| NPi-100 | NPi-100 | NeurOptics | Irvine | California | United States of America |
| NPi-200 | NPi-200 | NeurOptics | Irvine | California | United States of America |
| VIP-200 | VIP-200 | NeurOptics | Irvine | California | United States of America |
| PLR-200 | PLR-200 | NeurOptics | Irvine | California | United States of America |
| ForSite | ForSite digital pupillometer | NeurOptics | Irvine | California | United States of America |
| Neurolight | Neurolight | IDMed | Marseille |  | France |
| Neurolight v1.2 | Neurolight version 1.2 | IDMed | Marseille |  | France |
| IDMed | IDMed pupillometer type not otherwise specified, but monocular as specified by research methods | IDMed | Marseille |  | France |
| Algiscan | NeuroLight Algiscan | IDMed | Marseille |  | France |
| Applied sciences |  |  |  |  |  |

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