**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 |  |  |  |  |  |

**References:**

1. Papangelou A, Zink EK, Chang WW, et al. Automated Pupillometry and Detection of Clinical Transtentorial Brain Herniation: A Case Series. Mil Med 2018;183:e113-e121.

2. McNett M, Moran C, Janki C, Gianakis A. Correlations Between Hourly Pupillometer Readings and Intracranial Pressure Values. J Neurosci Nurs 2017;49:229-234.

3. Chen JW, Gombart ZJ, Rogers S, Gardiner SK, Cecil S, Bullock RM. Pupillary reactivity as an early indicator of increased intracranial pressure: The introduction of the Neurological Pupil index. Surg Neurol Int 2011;2:82.

4. McNett M, Moran C, Grimm D, Gianakis A. Pupillometry Trends in the Setting of Increased Intracranial Pressure. J Neurosci Nurs 2018;50:357-361.

5. Ong C, Hutch M, Barra M, Kim A, Zafar S, Smirnakis S. Effects of Osmotic Therapy on Pupil Reactivity: Quantification Using Pupillometry in Critically Ill Neurologic Patients. Neurocrit Care 2019;30:307-315.

6. Natzeder S, Mack DJ, Maissen G, Strassle C, Keller E, Muroi C. Portable Infrared Pupillometer in Patients With Subarachnoid Hemorrhage: Prognostic Value and Circadian Rhythm of the Neurological Pupil Index (NPi). J Neurosurg Anesthesiol 2018.

7. Jahns FP, Miroz JP, Messerer M, et al. Quantitative pupillometry for the monitoring of intracranial hypertension in patients with severe traumatic brain injury. Crit Care 2019;23:155.

8. Stevens AR, Su Z, Toman E, Belli A, Davies D. Optical pupillometry in traumatic brain injury: neurological pupil index and its relationship with intracranial pressure through significant event analysis. Brain Inj 2019;33:1032-1038.

9. Soeken TA, Alonso A, Grant A, et al. Quantitative Pupillometry for Detection of Intracranial Pressure Changes During Head-Down Tilt. Aerosp Med Hum Perform 2018;89:717-723.

10. Osman M, Stutzman SE, Atem F, et al. Correlation of Objective Pupillometry to Midline Shift in Acute Stroke Patients. J Stroke Cerebrovasc Dis 2019;28:1902-1910.

11. Thiagarajan P, Ciuffreda KJ. Pupillary responses to light in chronic non-blast-induced mTBI. Brain Inj 2015;29:1420-1425.

12. Capó-Aponte JE, Urosevich TG, Walsh DV, Temme LA, Tarbett AK. Pupillary Light Reflex as an Objective Biomarker for Early Identification of Blast-Induced mTBI. Journal of Spine 2013;S4:004.

13. Peinkhofer C, Martens P, Grand J, et al. Influence of Strategic Cortical Infarctions on Pupillary Function. Front Neurol 2018;9:916.

14. Raygor KP, Theodosopoulos PV. Use of the Neurological Pupil Index to Predict Postoperative Visual Function After Resection of a Tuberculum Sellae Meningioma: A Case Report. Cureus 2019;11:e5998.

15. Kim TJ, Ko SB. Implication of Neurological Pupil Index for Monitoring of Brain Edema. Acute Crit Care 2018;33:57-60.

16. Bartosova O, Bonnet C, Ulmanova O, et al. Pupillometry as an indicator of L-DOPA dosages in Parkinson's disease patients. J Neural Transm (Vienna) 2018;125:699-703.

17. Frost S, Robinson L, Rowe CC, et al. Evaluation of Cholinergic Deficiency in Preclinical Alzheimer's Disease Using Pupillometry. J Ophthalmol 2017;2017:7935406.

18. Kim HM, Yang HK, Hwang JM. Quantitative analysis of pupillometry in isolated third nerve palsy. PLoS One 2018;13:e0208259.

19. Aoun SG, Welch BG, Cortes M, et al. Objective Pupillometry as an Adjunct to Prediction and Assessment for Oculomotor Nerve Injury and Recovery: Potential for Practical Applications. World Neurosurg 2019;121:e475-e480.

20. Shirozu K, Murayama K, Karashima Y, Setoguchi H, Miura T, Hoka S. The relationship between seizure in electroconvulsive therapy and pupillary response using an automated pupilometer. J Anesth 2018;32:866-871.

21. Hasan S, Peluso L, Ferlini L, et al. Correlation Between Electroencephalography and Automated Pupillometry in Critically Ill Patients: A Pilot Study. J Neurosurg Anesthesiol 2019.

22. Rollins MD, Feiner JR, Lee JM, Shah S, Larson M. Pupillary effects of high-dose opioid quantified with infrared pupillometry. Anesthesiology 2014;121:1037-1044.

23. Ofte HK, von Hanno T, Alstadhaug KB. Reduced cranial parasympathetic tone during the remission phase of cluster headache. Cephalalgia 2015;35:469-477.

24. Riffard C, Viet TQ, Desgranges FP, et al. The pupillary light reflex for predicting the risk of hypotension after spinal anaesthesia for elective caesarean section. Anaesth Crit Care Pain Med 2018;37:233-238.

25. Rouche O, Wolak-Thierry A, Destoop Q, et al. Evaluation of the depth of sedation in an intensive care unit based on the photo motor reflex variations measured by video pupillometry. Ann Intensive Care 2013;3:5.

26. Wildemeersch D, Baeten M, Peeters N, Saldien V, Vercauteren M, Hans G. Pupillary dilation reflex and pupillary pain index evaluation during general anaesthesia: a pilot study. Rom J Anaesth Intensive Care 2018;25:19-23.

27. Isnardon S, Vinclair M, Genty C, Hebrard A, Albaladejo P, Payen JF. Pupillometry to detect pain response during general anaesthesia following unilateral popliteal sciatic nerve block: a prospective, observational study. Eur J Anaesthesiol 2013;30:429-434.

28. Aissou M, Snauwaert A, Dupuis C, Atchabahian A, Aubrun F, Beaussier M. Objective assessment of the immediate postoperative analgesia using pupillary reflex measurement: a prospective and observational study. Anesthesiology 2012;116:1006-1012.

29. Guglielminotti J, Mentre F, Gaillard J, Ghalayini M, Montravers P, Longrois D. Assessment of pain during labor with pupillometry: a prospective observational study. Anesth Analg 2013;116:1057-1062.

30. Wildemeersch D, Peeters N, Saldien V, Vercauteren M, Hans G. Pain assessment by pupil dilation reflex in response to noxious stimulation in anaesthetized adults. Acta Anaesthesiol Scand 2018.

31. Lukaszewicz AC, Dereu D, Gayat E, Payen D. The relevance of pupillometry for evaluation of analgesia before noxious procedures in the intensive care unit. Anesth Analg 2015;120:1297-1300.

32. Duale C, Julien H, Pereira B, Abbal B, Baud C, Schoeffler P. Pupil diameter during postanesthetic recovery is not influenced by postoperative pain, but by the intraoperative opioid treatment. J Clin Anesth 2015;27:23-32.

33. Kantor E, Montravers P, Longrois D, Guglielminotti J. Pain assessment in the postanaesthesia care unit using pupillometry: A cross-sectional study after standard anaesthetic care. Eur J Anaesthesiol 2014;31:91-97.

34. Vinclair M, Schilte C, Roudaud F, et al. Using Pupillary Pain Index to Assess Nociception in Sedated Critically Ill Patients. Anesth Analg 2019;129:1540-1546.

35. Charier D, Vogler MC, Zantour D, et al. Assessing pain in the postoperative period: Analgesia Nociception Index(TM)versus pupillometry. Br J Anaesth 2019;123:e322-e327.

36. Paulus J, Roquilly A, Beloeil H, Theraud J, Asehnoune K, Lejus C. Pupillary reflex measurement predicts insufficient analgesia before endotracheal suctioning in critically ill patients. Crit Care 2013;17:R161.

37. Guglielminotti J, Grillot N, Paule M, et al. Prediction of movement to surgical stimulation by the pupillary dilatation reflex amplitude evoked by a standardized noxious test. Anesthesiology 2015;122:985-993.

38. Jakuscheit A, Weth J, Lichtner G, Jurth C, Rehberg B, von Dincklage F. Intraoperative monitoring of analgesia using nociceptive reflexes correlates with delayed extubation and immediate postoperative pain: A prospective observational study. Eur J Anaesthesiol 2017;34:297-305.

39. Vinclair M, Roudaud F, Francony G, Payen JF. Quantitative pupillometry to assess nociception in a sedated patient with hemispheric cerebral infarction. Eur J Anaesthesiol 2017;34:316-318.

40. Yang E, Kreuzer M, Hesse S, Davari P, Lee SC, Garcia PS. Infrared pupillometry helps to detect and predict delirium in the post-anesthesia care unit. J Clin Monit Comput 2018;32:359-368.

41. Belani KG, Sessler DI, Larson MD, et al. The pupillary light reflex. Effects of anesthetics and hyperthermia. Anesthesiology 1993;79:23-27.

42. Mullaguri N, Katyal N, Sarwal A, et al. Pitfall in Pupillometry: Exaggerated Ciliospinal Reflex in a Patient in Barbiturate Coma Mimicking a Nonreactive Pupil. Cureus 2017;9:e2004.

43. Stoops WW, Glaser PE, Rush CR. Miotic and subject-rated effects of therapeutic doses of tapentadol, tramadol, and hydromorphone in occasional opioid users. Psychopharmacology (Berl) 2013;228:255-262.

44. Stoops WW, Lofwall MR, Nuzzo PA, Craig LB, Siegel AJ, Walsh SL. Pharmacodynamic profile of tramadol in humans: influence of naltrexone pretreatment. Psychopharmacology (Berl) 2012;223:427-438.

45. Nielsen AG, Pedersen RS, Noehr-Jensen L, Damkier P, Brosen K. Two separate dose-dependent effects of paroxetine: mydriasis and inhibition of tramadol's O-demethylation via CYP2D6. Eur J Clin Pharmacol 2010;66:655-660.

46. Brokjaer A, Olesen AE, Kreilgaard M, et al. Objective markers of the analgesic response to morphine in experimental pain research. J Pharmacol Toxicol Methods 2015;73:7-14.

47. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. Addiction 2011;106:1460-1473.

48. Tylleskar I, Skulberg AK, Skarra S, Nilsen T, Dale O. Pharmacodynamics and arteriovenous difference of intravenous naloxone in healthy volunteers exposed to remifentanil. Eur J Clin Pharmacol 2018;74:1547-1553.

49. Skulberg AK, Tylleskar I, Nilsen T, et al. Pharmacokinetics and -dynamics of intramuscular and intranasal naloxone: an explorative study in healthy volunteers. Eur J Clin Pharmacol 2018;74:873-883.

50. Kongsgaard UE, Hoiseth G. Dynamic assessment of the pupillary reflex in patients on high-dose opioids. Scand J Pain 2019;19:465-471.

51. Hysek CM, Liechti ME. Effects of MDMA alone and after pretreatment with reboxetine, duloxetine, clonidine, carvedilol, and doxazosin on pupillary light reflex. Psychopharmacology (Berl) 2012;224:363-376.

52. Haddock JH, Mercante DE, Paccione R, et al. Use of Digital Pupillometry to Measure Sedative Response to Propofol. Ochsner J 2017;17:250-253.

53. Eilers H, Larson MD. The effect of ketamine and nitrous oxide on the human pupillary light reflex during general anesthesia. Auton Neurosci 2010;152:108-114.

54. Noehr-Jensen L, Zwisler ST, Larsen F, et al. Impact of CYP2C19 phenotypes on escitalopram metabolism and an evaluation of pupillometry as a serotonergic biomarker. Eur J Clin Pharmacol 2009;65:887-894.

55. Koller D, Belmonte C, Lubomirov R, et al. Effects of aripiprazole on pupillometric parameters related to pharmacokinetics and pharmacogenetics after single oral administration to healthy subjects. J Psychopharmacol 2018;32:1212-1222.

56. Shirozu K, Setoguchi H, Tokuda K, et al. The effects of anesthetic agents on pupillary function during general anesthesia using the automated infrared quantitative pupillometer. J Clin Monit Comput 2017;31:291-296.

57. Theodossiadis PG, Achtsidis V, Theodoropoulou S, Tentolouris N, Komninos C, Fountas KN. The effect of alpha antagonists on pupil dynamics: implications for the diagnosis of intraoperative floppy iris syndrome. Am J Ophthalmol 2012;153:620-626.

58. Bradley JC, Bentley KC, Mughal AI, Bodhireddy H, Young RS, Brown SM. The effect of gender and iris color on the dark-adapted pupil diameter. J Ocul Pharmacol Ther 2010;26:335-340.

59. Wilson MH, Edsell M, Imray C, Wright A, Birmingham Medical Research Expeditionary S. Changes in pupil dynamics at high altitude--an observational study using a handheld pupillometer. High Alt Med Biol 2008;9:319-325.