Table 2 Summary of preclinical and clinical trial studies on seven promising adjunct neuroprotective agents

Adjunct therapy	Mode of action	Examples of recent preclinical trials	Clinical RCTs
Melatonin	Endogenous hormone which entrains the circadian rhythm at physiological doses. At high pharmacological doses melatonin is a powerful antioxidant and antiapoptotic agent.	Systematic review and meta-analysis of 400 adult rodents showed a 43% reduction in stroke infarct size with melatonin.[74] A piglet study showed augmentation of brain protection with high dose melatonin at 10 min and cooling versus cooling alone.[75]	Oral melatonin (10 mg/kg/day 5 doses) tablets crushed in 5 mL distilled water. n=15 cooled, n=15 cooled plus melatonin, n=15 controls.[76]
Erythropoietin (Epo)	*Acute actions*: neurotrophic, anti-inflammatory, antiapoptotic, antioxidant *Chronic actions*: erythropoiesis, angiogenesis, oligodendrogenesis, neurogenesis.	Non-human primate model—hypothermia+Epo treatment improved outcomes in non-human primates exposed to umbilical cord occlusion.[77]	NEAT trial—safety and PK.[78] Phase II trial of hypothermia and Epo showed less MRI injury and better short-term outcome.[79] Phase III trial is now underway in the USA.
Xenon	Inhibits NMDA signalling, antiapoptotic.	Preclinical piglet studies showed benefit of combined cooling and xenon compared with no treatment.[80 81]	No evidence of short-term benefit with xenon and cooling above cooling alone, using MRS lactate/NAA as a surrogate outcome.[82]
Argon	GABA agonist and oxygen type properties. Antiapoptotic.	Preclinical piglet study showed brain protection on MRS and histology with 50% argon and cooling compared with cooling alone.[83]	Phase II trials pending regulatory approval.
Allopurinol	Reduces free radical production and in high doses acts as a free radical scavenger and free iron chelator.	Improved ^{31}P MRS metabolites and MRI values with allopurinol in piglets.[84]	ALBINO trial to start in Europe 2017—to assess benefit of early allopurinol at 30 min plus cooling versus cooling alone.
Stem cells	Paracrine signalling—not cellular integration or direct proliferative effects.	Evidence of improved neurological outcome and reduced histological injury.[85]	Autologous umbilical cord cells in HIE demonstrated feasibility.[86]
Magnesium	Prevention of excitatory injury by stabilisation of neuronal membranes and blockade of excitatory neurotransmitters, for example, glutamate.	Magnesium alone has not been protective in piglet models of hypoxia.[87] Combinations of magnesium with cooling has shown benefit.[88]	Recent meta-analysis shows no evidence of benefit.[88] A multicentre pilot RCT reported safety but no outcome data, larger RCT to follow[89]

HIE, hypoxic-ischaemic encephalopathy; GABA, gamma-aminobutyric acid; MRS, magnetic resonance spectroscopy; NAA, N-acetylasparate; NMDA, N-methyl-D-aspartate; PK, pharmacokinetics; RCT, randomised controlled trials.