注意	レボメプロマジン	相互に中枢神経抑制作用↑ 減量するなど慎重に投与する。抗痙攣作用は増強されることはないので抗痙攣剤は減量してはならない。	相加作用
注意	ロフェプラミン	中枢神経抑制作用↑	相加作用

併用薬剤名

マプロチリン

関連キーワード:
四環系抗うつ薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	フルトプラゼパム	(1)眠気、注意力・集中力・反射運動能力等の低下 (2)併用中のフルトプラゼパムを急速に減量又は中止すると痙攣発作が起こるおそれがある。	(1)相加作用 (2)フルトプラゼパムの抗痙攣作用により抑制されていたマプロチリンの痙攣誘発作用がフルトプラゼパムの減量・中止によりあらわれることが考えられている。
注意	クロルジアゼポキシド	眠気、注意力・集中力・反射運動能力等↓	相加作用
注意	クロルジアゼポキシド	マプロチリンと併用しているクロルジアゼポキシドを急速に減量又は中止すると痙攣発作がおこる可能性がある。	クロルジアゼポキシドの抗痙攣作用により抑制されていたマプロチリンの痙攣誘発作用がクロルジアゼポキシドの減量・中止によりあらわれることが考えられている。
注意	エスタゾラム	1)眠気、注意力・集中力・反射運動能力等↓ 2)併用中のエスタゾラムを急速に減量又は中止すると痙攣発作がおこる可能性がある 。	1)相加作用 2)エスタゾラムの抗痙攣作用により抑制されていたマプロチリンの痙攣誘発作用がエスタゾラムの減量・中止によりあらわれることが考えられている 。
注意	ジアゼパム	1) 眠気、注意力・集中力・反射運動能力等の低下 2) 併用中のジアゼパムを急速に減量又は中止により痙攣発作	1)相加作用 2) ジアゼパムの抗痙攣作用により抑制されていたマプロチリンの痙攣誘発作用がジアゼパムの減量・中止によりあらわれることが考えられている 。
注意	ロラゼパム	(1)眠気、注意力・集中力・反射運動能力等↓ (2)併用中のロラゼパムを急速に減量又は中止すると痙攣発作が起こるおそれがある。	(1)相加作用 (2)ロラゼパムの抗痙攣作用により抑制されていたマプロチリンの痙攣誘発作用がロラゼパムの減量・中止によりあらわれることが考えられている。
注意	ロルメタゼパム	1)眠 気、注意力・集中力・反射運動能力等↓ 2)併用中のロルメタゼパムを急速に減量又は中止すると痙攣発作がおこる可能性がある。	1)相加作用 2)ロルメタゼパムの抗痙攣作用により抑制されていたマプロチリンの痙攣誘発作用がロルメタゼパムの減量・中止によりあらわれることが考えられている。

注意	フルタゾラム	併用中のフルタゾラムを急速に減量又は中止すると痙攣発作が起こるおそれがある。	フルタゾラムの抗痙攣作用が、四環系抗うつ剤による痙攣発作の発現を抑えている可能性がある。
注意	フェノバルビタール	(1)相互に作用↑ (2)これらの抗うつ剤の血中濃度↓ 減量するなど注意すること。	(1)相加作用 (2) フェノバルビタールの肝薬物代謝酵素誘導作用による。
注意	ロフラゼプ酸エチル	併用中のロフラゼプ酸エチルを急速に減量又は中止すると痙攣発作が起こるおそれがある。	ロフラゼプ酸エチルの抗痙攣作用が、四環系抗うつ剤による痙攣発作の発現を抑えている可能性がある。

併用薬剤名

ミコナゾール

関連キーワード:
CYP3A4 阻害作用を有する薬剤
アゾール系抗真菌薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
禁忌	トリアゾラム	トリアゾラムの作用↑及び作用時間↑	どちらもCYP3A4で代謝されるため、トリアゾラムの代謝↓血中濃度↑
注意	ブロチゾラム	ブロチゾラムの作用↑作用時間↑	ミコナゾールで代謝酵素CYP3A4が阻害され、、ブロチゾラムの血中濃度↑

併用薬剤名

ミルナシプラン

関連キーワード:
セロトニン再取り込み阻害作用を有する薬剤

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	イミプラミン	セロトニン症候群のおそれあり。	相加作用
注意	クロミプラミン	セロトニン症候群のおそれあり。	相加作用
注意	タンドスピロン	セロトニン症候群のおそれあり。	相加作用

併用薬剤名

メキシレチン

関連キーワード:
抗不整脈薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	フルボキサミン	メキシチレンの血中濃度↑ メキシレチンを減量するなどして注意して使用する。	メキシチレンの血中濃度↑or 半減期↑or AUC↑

併用薬剤名

メチルフェニデート

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	イミプラミン	イミプラミンの作用↑	イミプラミンの肝代謝↓、血中濃度↑
注意	クロミプラミン	クロミプラミンの血中濃度↑	代謝↓
注意	フェノバルビタール	フェノバルビタールの血中濃度↑ 減量するなど注意すること。	メチルフェニデートが肝代謝を抑制すると考えられている。
注意	マプロチリン	三環系抗うつ剤(イミプラミン)で作用↑	代謝↓
注意	ロフェプラミン	他の三環系抗うつ薬(イミプラミン)で作用↑の報告がある。	代謝↓、血中濃度↑

併用薬剤名

ピロカルピン

関連キーワード:
コリン作動薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	スルピリド	内分泌機能調節異常又は錐体外路症状	相加作用
注意	ゾテピン	内分泌機能調節異常又は錐体外路症状	相加作用
注意	チアプリド	内分泌機能調節異常又は錐体外路症状	相加作用
注意	チミペロン	内分泌機能調節異常又は錐体外路症状	相加作用
注意	デカン酸フルフェナジン	内分泌機能調節異常又は錐体外路症状	相加作用
注意	トリフロペラジン	内分泌機能調節異常又は錐体外路症状	相加作用
注意	ピモジド	内分泌機能調節異常又は錐体外路症状	相加作用
注意	フルフェナジン	内分泌機能調節異常又は錐体外路症状	相加作用

注意	プロクロルペラジン	内分泌機能調節異常又は錐体外路症状観察を十分に行い，慎重に投与する。	相加作用
注意	プロペリシアジン	内分泌機能調節異常又は錐体外路症状観察を十分に行い，慎重に投与する。	相加作用
注意	ブロムペリドール	内分泌機能調節異常又は錐体外路症状	相加作用
注意	ペルフェナジン	内分泌機能調節異常又は錐体外路症状	相加作用
注意	ペロスピロン	内分泌機能調節異常又は錐体外路症状	相加作用
注意	モサプラミン	内分泌機能調節異常又は錐体外路症状	相加作用
注意	レボメプロマジン	内分泌機能調節異常又は錐体外路症状	相加作用

併用薬剤名

メトプロロール

関連キーワード:
降圧薬
抗不整脈薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	パロキセチン	重度の血圧低下が報告されている。	メトプロロールの(S)-体及び(R)-体のT1/2↑、AUC↑

併用薬剤名

薬物代謝酵素(主にCYP3A4)を誘導する薬剤

例)
カルバマゼピン
リファンピシン　　など

関連キーワード:
CYP3A4 阻害作用を有する薬剤

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	デカン酸ハロペリドール	デカン酸ハロペリドールの作用↓	薬物代謝酵素誘導作用により，デカン酸ハロペリドールの血中濃度↓
注意	ハロペリドール	ハロペリドールの作用↓	薬物代謝酵素誘導作用により，ハロペリドールの血中濃度↓

併用薬剤名

四環系抗うつ薬

例）
マプロチリン　　など

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	フルタゾラム	併用中のフルタゾラムを急速に減量又は中止すると痙攣発作が起こるおそれがある。	フルタゾラムの抗痙攣作用が、四環系抗うつ剤による痙攣発作の発現を抑えている可能性がある。
注意	フェノバルビタール	(１)相互に作用↑ (２)これらの抗うつ剤の血中濃度↓ 減量するなど注意すること。	(１)相加作用 (２)フェノバルビタールの肝薬物代謝酵素誘導作用による。
注意	ロフラゼプ酸エチル	併用中のロフラゼプ酸エチルを急速に減量又は中止すると痙攣発作が起こるおそれがある。	ロフラゼプ酸エチルの抗痙攣作用が、四環系抗うつ剤による痙攣発作の発現を抑えている可能性がある。

併用薬剤名

リスペリドン

関連キーワード:
抗精神病薬
抗ドパミン作用を有する薬剤
非定型抗精神病薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	パロキセチン	悪性症候群があらわれるおそれあり。 過鎮静、錐体外路症状等。	リスペリドン及び活性代謝物の血中濃度↑
注意	マプロチリン	マプロチリンの血中濃度↑	リスペリドンによってマプロチリンの代謝が阻害され、マプロチリンの血中濃度↑

併用薬剤名

リトナビル

関連キーワード:
CYP3A4 阻害作用を有する薬剤
HIV プロテアーゼ阻害剤
抗 HIV 薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	アミトリプチリン	アミトリプチリンの作用↑	CYP3A4阻害作用によりアミトリプチリンの代謝↓により血中濃度↑
注意	アルプラゾラム	中枢神経抑制作用↑	アルプラゾラムの代謝↓で、AUC↑、クリアランス↑、半減期↑
禁忌	エスタゾラム	過度の鎮静や呼吸抑制等	CYPに対する競合的阻害により 、エスタゾラムの血中濃度↑
禁忌	クアゼパム	過度の鎮静や呼吸抑制	リトナビルのチトクロームP450に対する競合的阻害作用により，併用した場合，クアゼパムの血中濃度が大幅に上昇することが予測される.
禁忌	クロラゼプ酸二カリウム	過度の鎮静や呼吸抑制	CYP3A阻害により，クロラゼプ酸二カリウムの代謝↓血中濃度↑
禁忌	ジアゼパム	過度の鎮静や呼吸抑制等	CYP阻害により、ジアゼパムの血中濃度↑
注意	トラゾドン	トラゾドンの血中濃度↑ トラゾドンを減量するなど用量に注意すること。	トラゾドンの代謝↓
禁忌	トリアゾラム	トリアゾラムの作用↑及び作用時間↑	どちらもCYP3A4で代謝されるため、トリアゾラムの代謝↓血中濃度↑
禁忌	ピモジド	QT延長、心室性不整脈等	代謝阻害により、ピモジドの血中濃度↑
禁忌	フルラゼパム	過度の鎮静や呼吸抑制	CYPに対する競合的阻害作用により、フルラゼパムの血中濃度↑
禁忌	ミダゾラム	過度の鎮静や呼吸抑制	CYP3A4阻害により、ミダゾラムの血中濃度↑

併用薬剤名

利尿薬

例）
チアジド系降圧利尿薬　　など

関連キーワード:
降圧薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	バルビタール	起立性低血圧↑ 減量するなど注意する。	機序は不明
注意	フェノバルビタール	起立性低血圧が増強されることがある。 減量するなど注意すること。	機序は不明であるが、高用量のフェノバルビタールは血圧を低下させることがある。

併用薬剤名
リネゾリド

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	パロキセチン	セロトニン症候群等のセロトニン作用による症状があらわれることがある。これらの薬物を併用する際には観察を十分に行うこと。	相加作用

併用薬剤名
リファンピシン **関連キーワード:** **CYP1A2 誘導作用を有する薬剤** **CYP3A4 誘導作用を有する薬剤** **肝酵素誘導作用をもつ薬剤**

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	イミプラミン	イミプラミンの血中濃度↓	肝酵素誘導作用による。
注意	オランザピン	オランザピンの作用↓	CYP1A2 誘導作用により、オランザピンのクリアランス↑、血中濃度↓
注意	クエチアピン	クエチアピンの作用↓	CYP3A4 の誘導により、クエチアピンのクリアランス↑（外国人でクリアランスが約 5 倍↑、Cmax が 66%↓、AUC が 80%↓）
注意	クロミプラミン	クロミプラミンの血中濃度↓	肝酵素誘導作用による。
注意	ゾピクロン	ゾピクロンの作用↓	CPY3A4 誘導により、ゾピクロンの代謝↑
注意	ゾルピデム	ゾルピデムの作用↓	CYP3A4 の誘導によりゾルピデムの代謝↑、血中濃度↓
注意	デカン酸ハロペリドール	デカン酸ハロペリドールの作用↓	薬物代謝酵素誘導作用により，デカン酸ハロペリドールの血中濃度↓
注意	トリアゾラム	トリアゾラムの作用↓	トリアゾラムの代謝↑
注意	ノルトリプチリン	ノルトリプチリンの作用↓	ノルトリプチリンの代謝↑
注意	パロキセチン	パロキセチンの作用↓	パロキセチンの血中濃度↓
注意	ハロペリドール	ハロペリドールの作用↓	薬物代謝酵素誘導作用により，ハロペリドールの血中濃度↓
注意	ミダゾラム	ミダゾラムの作用↓	酵素誘導により、ミダゾラムの代謝↑
注意	ロフェプラミン	他の三環系抗うつ薬（イミプラミン）の血中濃度↓の報告がある。	肝薬物代謝酵素誘導作用によるロフェプラミンの代謝促進で血中濃度↓

併用薬剤名

レボドパ製剤

関連キーワード:
抗パーキンソン病薬
ドパミン作動薬

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	オランザピン	相互に作用↓	拮抗作用
注意	カルピプラミン	相互に作用↓	拮抗作用
注意	クロカプラミン	相互に作用↓	拮抗作用
注意	クロルプロマジン	相互に作用↓	拮抗作用
注意	スルトプリド	相互に作用↓	拮抗作用
注意	スルピリド	相互に作用↓	拮抗作用
注意	スルピリド	相互に作用↓	拮抗作用
注意	ゾテピン	相互に作用↓	拮抗作用
注意	チアプリド	相互に作用↓	拮抗作用
注意	チミペロン	相互に作用↓	拮抗作用
注意	デカン酸ハロペリドール	相互に作用↓	拮抗作用
注意	デカン酸フルフェナジン	相互に作用↓	拮抗作用
注意	トリフロペラジン	相互に作用↓	拮抗作用
注意	ハロペリドール	相互に作用↓	拮抗作用
注意	ピモジド	相互に作用↓	拮抗作用
注意	フルフェナジン	相互に作用↓	拮抗作用
注意	プロクロルペラジン	相互に作用↓ 投与量を調節するなど慎重に投与する。	拮抗作用
注意	プロペリシアジン	相互に作用↓ 投与量を調節するなど慎重に投与する。	拮抗作用
注意	ブロムペリドール	ドパミン作動薬の作用↓	拮抗作用
注意	ペルフェナジン	相互に作用↓	拮抗作用
注意	ペロスピロン	相互に作用↓	拮抗作用
注意	モサプラミン	相互に作用↓	拮抗作用
注意	レボメプロマジン	相互に作用↓	拮抗作用

併用薬剤名

レボメプロマジン

関連キーワード:
抗精神病薬
フェノチアジン系薬剤

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	イミプラミン	抗コリン作用↑ 中枢神経抑制作用↑	相加作用

注意	クロミプラミン	抗コリン作用↑ 中枢神経抑制作用↑	相加作用
注意	マプロチリン	鎮静、抗コリン作用↑	相加作用

併用薬剤名

ワルファリン

関連キーワード:
クマリン系抗凝血薬
止血・血液凝固を阻害する薬剤
出血傾向が増強する薬剤

併用情報	一般名	臨床症状・対処	機序 ・ 危険因子
注意	アミトリプチリン	クマリン系抗凝固薬の作用↑	アミトリプチリンの肝薬物代謝酵素阻害作用により、クマリン系抗凝固薬の代謝↓
注意	イミプラミン	クマリン系抗凝血剤の血中濃度半減期↑	機序不明。他の三環系抗うつ薬(ノルトリプチリン)で報告あり。
注意	クロミプラミン	クマリン系抗凝血剤の血中濃度半減期↑	機序不明。他の三環系抗うつ剤(ノルトリプチリン)で報告あり。
注意	セルトラリン	ワルファリンのプロトロンビン反応時間↑(AUCが8%増)の報告あり。セルトラリンの投与を開始もしくは中止する場合は、プロトロンビン時間を慎重にモニターすること。	機序不明
注意	セルトラリン	異常出血(鼻出血、胃腸出血、血尿等)注意して投与する。	SSRIによって血小板凝集能が阻害される。
注意	トラゾドン	プロトロンビン時間↓	機序不明
注意	トリクロホスナトリウム	クマリン系抗凝血剤の作用↑ 通常より頻回にプロトロンビン値の測定を行うなど慎重に投与する。	トリクロホスナトリウムの主代謝産物であるトリクロル酢酸が血漿蛋白結合部位からワルファリンを遊離置換し、遊離型ワルファリン濃度を増加させる。
注意	ノルトリプチリン	クマリン系抗凝血剤の血中濃度半減期↑	ワルファリンの肝代謝↓
注意	バルビタール	クマリン系抗凝血剤の作用↓ 通常より頻回に血液凝固時間の測定を行い、クマリン系抗凝血剤の量を調整する。	バルビタールの肝薬物代謝酵素誘導作用によって、半減期↓
注意	パロキセチン	他の抗うつ剤でクマリン系抗凝固薬の作用↑	パロキセチンとの相互作用は認められていない。
注意	パロキセチン	出血傾向↑	相加作用
注意	フェノバルビタール	クマリン系抗凝血剤の作用↓ 通常より頻回に血液凝固時間の測定を行い、クマリン系抗凝血剤の用量を調整する。	フェノバルビタールの肝薬物代謝酵素誘導作用による。
注意	フルボキサミン	ワルファリンの血中濃度↑ or 半減期↑ or AUC↑ プロトロンビン時間を測定し、ワルファリンの用量を調節するなど、注意して投与すること。	ワルファリンの代謝↓

注意	フルボキサミン	皮膚の異常出血(斑状出血、紫斑等)、出血症状(胃腸出血等)	SSRIの血小板凝集阻害が相加され、出血傾向↑
注意	ペントバルビタール	抗凝血作用↓ 頻回にプロトロンビン値の測定を行い、ワルファリンカリウムの用量を調節する。	ワルファリンカリウムの代謝↑、半減期↓、クリアランス↑
注意	ペントバルビタール	抗凝血作用↓ 頻回にプロトロンビン値の測定を行い、ワルファリンカリウムの用量を調節する。	ワルファリンカリウムの代謝↑、半減期↓、クリアランス↑
注意	抱水クロラール	クマリン系抗凝固剤の作用↑ 通常より頻回にプロトロンビン値の測定を行うなど慎重に投与する。	抱水クロラールは血漿たん白に結合したクマリン系抗凝固血剤を遊離させる。
注意	マプロチリン	クマリン系抗凝血剤の血中濃度半減期↑	機序不明。他の三環系抗うつ薬(ノルトリプチリン)で報告がある。

Ⅲ．研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Enomoto M, Endo T, Higuchi S, Miura N, Nakano Y, Kohtoh S, Taguchi Y, Suenaga K, Aritake S, Matsuura M, Mishima K	Newly Developed Waist Actigraphy and its Sleep/Wake Scoring Algorithm.	Sleep and Biological Rhythms			2009
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三島和夫	日本における向精神薬の処方実態 ーベンゾジアゼピン系薬物を中心に	医学のあゆみ	236	968-974	2011
三島和夫	生活習慣病の治療と予防における睡眠医療のあり方	医学のあゆみ	236	5-10	2011

Ⅳ. 研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Newly developed waist actigraphy and its sleep/wake scoring algorithm

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Abstract

The purpose of this study was to formulate an algorithm for assessing sleep/waking from activity intensities measured with a waist-worn actigraphy, the Lifecorder PLUS (LC; Suzuken Co. Ltd., Nagoya, Japan), and to test the validity of the algorithm. The study consisted of 31 healthy subjects (M/F = 20/11, mean age 31.7 years) who underwent one night of simultaneous measurement of activity intensity by LC and polysomnography (PSG). A sleep(S)/wake(W) scoring algorithm based on a linear model was determined through discriminant analysis of activity intensities measured by LC over a total of 235 h and 56 min and the corresponding PSG-based S/W data. The formulated S/W scoring algorithm was then used to score S/W during the monitoring epochs (2 min each, 7078 epochs in total) for each subject. The mean agreement rate with the corresponding PSG-based S/W data was 86.9%, with a mean sensitivity (sleep detection) of 89.4% and mean specificity (wakefulness detection) of 58.2%. The agreement rates for the individual stages of sleep were 60.6% for Stage 1, 89.3% for Stage 2, 99.2% for Stage 3 + 4, and 90.1% for Stage REM. These results demonstrate that sleep/wake activity in young to middle-aged healthy subjects can be assessed with a reliability comparable to that of conventional actigraphy through LC waist actigraphy and the optimal S/W scoring algorithm.

Key words: actigraphy, polysomnography, sleep/wake scoring algorithm, sleep-waking, waist-worn.

INTRODUCTION

An actigraphy is a small lightweight device for non-invasive and continuous monitoring of human rest/activity (sleep/wake) cycles.[1,2] The most commonly used actigraphy in current sleep research is a unit that is worn on the non-dominant wrist like a wristwatch for continuous measurement of forearm motor activity. The actigraphy unit generally consists of a piezoelectric accelerometer and a memory for storing the measured values for a specific time epoch, typically from 1 s to several minutes.

Algorithms using the activity level measured by the actigraphy to determine whether the person wearing the unit is awake or asleep during the time epoch have been developed for use with individual actigraphy units.[3–5] Studies to date investigating the agreement rate of polysomnography (PSG) and various actigraphy units in

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healthy adults have reported a very high agreement rate of 85 to 96% between the two methods with use of the optimal specific sleep/wake scoring algorithm.[3–7]

Although actigraphy is suitable for assessment of sleep/wake activity during a specific time epoch, it cannot be used independently for confirmation or diagnosis of sleep disturbances because, contrary to PSG, it does not allow for collection of data on electro-oculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), and breathing function during sleep.[7] On the other hand, it has a distinct advantage over PSG in that it allows for continuous recording of rest/activity (sleep/wake state) over long periods of time outside of the sleep lab with minimal disruption to the subject's normal life. It is therefore commonly used in human sleep physiology research and clinical studies in patients with insomnia and circadian rhythm sleep disorders.[6] Future beneficial applications of actigraphy include sleep disturbance screening in a large number of subjects and evaluation of the effectiveness and side effects of drug and non-drug therapies requiring continuous assessment of sleep/wake activity. Inexpensive multipurpose devices providing a favorable cost–benefit balance in the clinical setting are, however, necessary to realize these new potential applications. There have been a few previous studies that assessed sleep/wake activity using an actigraphy placed on the trunk[8,9] and the head[10] because the current mainstream wrist-worn actigraphy unit cannot be readily used in individuals with upper dystaxia, individuals with involuntary movement such as finger tremors, and children and dementia patients who may inadvertently interfere with the device. Most are also not waterproof and cannot thus readily be used in individuals whose work involves handling of water. So actigraphy units that can be worn on body sites other than the wrist, such as the trunk, are still needed.

We therefore focused our research on an inexpensive activity monitor that is worn around the waist to measure activity as a new actigraphy option in sleep research and sleep medicine. In our study, data obtained from healthy adults was used to formulate an algorithm to score sleep/waking measured by waist actigraphy and test the validity of the algorithm.

METHODS

Features of waist actigraphy

An inexpensive activity monitor that is worn around the waist (Lifecorder PLUS [LC]; Suzuken Co. Ltd., Nagoya, Japan; ¥14800 = €100 = $128) was used to measure activity level during sleep. The LC was originally developed for measurement of daytime physical-activity level and has been used for the assessment of physical-activity-related energy expenditure.[11,12] The LC measures acceleration along the longitudinal axis every 4 s with an internal piezoelectric accelerometer and classifies the intensity into 11 levels from 0 to 9 (0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9) every 2 min.[11] Level 0 (corresponding to <0.06 G) denotes immobility and Levels 0.5 to 9 (corresponding to ≥0.06 G) denote subtle to strong movements. The cut-off point of activity intensity (the acceleration value) for each level is not provided by the manufacturer. It is possible to continuously record the activity intensity level with the time information for at least 2 months. After the completion of measurement, the recorded activity intensity data can be downloaded to a personal computer through a USB cable. The scoring algorithm was formulated from these data.

Experimental subjects

The study consisted of 31 healthy adults (20 males and 11 females with a mean age of 31.6 ± 10.4 years). Monitoring was performed by the Sleep Electroencephalography Lab at Aoki Hospital and the Sleep/Biological Rhythm Monitoring Unit of the National Institute of Mental Health of the National Center of Neurology and Psychiatry. Subjects underwent simultaneous continuous monitoring of intensity of physical movement during sleep by PSG and LC. The study was approved by the ethics committee of the National Center of Neurology and Psychiatry. Subjects were informed of the purposes and methods of the study and gave written consent to participate in the investigation.

PSG and LC recordings

The PSG consisted of measurement of a standard electroencephalogram (C3-A2, C4-A1, O1-A2, O2-A1), EOG, chin EMG, ECG, breathing function, and tibialis anterior EMG data every 30 s. The Polymate 1524 (TEAC Corporation, Tokyo, Japan) and Comet PSG (Grass-Technologies, RI, USA) were used for the PSG. The sleep stage (Stage 1, Stage 2, Stage 3 + 4, Stage REM or Stage wake) was then determined every 30 s according to the rules of Rechtschaffen and Kales.[13] Four consecutive 30-s intervals of sleep stage data were used to assess sleep/wake state every 2 min to correspond with the intervals with LC data. When four consecutive data contained two or more of Stage wake, the data set was classified as wake (W_{PSG}) according to the definition

adopted the previous studies.[14–16] All other data sets were classified as sleep (S_{PSG}). Furthermore, S_{PSG} was subclassified as Stage REM, Stage 1, Stage 2, or Stage 3 + 4, according to the most frequent sleep stage in the data set (e.g. when S_{PSG} contained two or more Stage 1 data, it was classified as Stage 1). However, when S_{PSG} contained two of two different stages, the priority order (Stage REM → Stage 1 → Stage 2 → Stage 3 + 4) was used (e.g. when S_{PSG} contained two Stage 1 and two Stage REM, it was classified as Stage REM).

Formulation of an algorithm for assessing sleep/waking

A S/W scoring algorithm for LC was newly formulated by the discriminant analysis. The data used for the development were the datasets of S_{PSG} (=0) and W_{PSG} (=1) corresponding to the LC exercise intensities obtained from 7078 epochs obtained from 31 subjects on 31 nights over a total of 235 h and 56 min.

Taking the S/W algorithm for the present actigraphy into account, we assume the five-dimension linear model that incorporates the exercise intensities during 10 min with the center of the time epoch of interest. The activity intensities 4 min before the scored epoch, 2 min before the scored epoch, during the scored epoch, 2 min after the scored epoch, and 4 min after the scored epoch were represented by x_1, x_2, x_3, x_4, and x_5, respectively. A linear discriminant function was given as the following equation for an arbitrary set of weight coefficients of a_1, a_2, a_3, a_4, and a_5.

$$z = a_1x_1 + a_2x_2 + a_3x_3 + a_4x_4 + a_5x_5$$

Where the variable of z can be used as the discriminant score to classify a set of activity intensities into the stage of S_{LC} or W_{LC}.

The above discriminant function was determined by the discriminant analysis. Supposing that the LC activity intensity in sleeping status and in waking status are categorized in class 1 and 2, respectively, and the number of the datasets in each class is set to n_1 and n_2, the i-th ($i = 1$ to n_k) variable in class k ($k = 1, 2$), $z_i^{(k)}$ is given as

$$z_i^{(k)} = a_1x_{1i}^{(k)} + a_2x_{2i}^{(k)} + a_3x_{3i}^{(k)} + a_4x_{4i}^{(k)} + a_5x_{5i}^{(k)}.$$

The variation of $\{z_i^{(k)}\}$ is represented by the total sum of squares, S_T, which can be decomposed to the between sum of squares, S_B, and the within sum of the squares, S_W ($S_T = S_B + S_W$).

$$S_T = \sum_{k=1}^{2}\sum_{i=1}^{n_k}(z_i^{(k)} - \bar{z})^2$$

$$S_B = \sum_{k=1}^{2} n_k(\bar{z}^{(k)} - \bar{z})^2$$

$$S_W = \sum_{k=1}^{2}\sum_{i=1}^{n_k}(z_i^{(k)} - \bar{z}^{(k)})^2.$$

Since the better discriminability between the two classes using z is equivalent to the increase of the ratio of correlation, $\eta^2 = S_B / S_T$, the set of weight coefficients, $\hat{a}_1$, $\hat{a}_2$, $\hat{a}_3$, $\hat{a}_4$, $\hat{a}_5$, that gives the maximum η^2 can be calculated by the following equations:

$$\begin{bmatrix} s_{11} & s_{12} & s_{13} & s_{14} & s_{15} \\ s_{21} & s_{22} & s_{23} & s_{24} & s_{25} \\ s_{31} & s_{32} & s_{33} & s_{34} & s_{35} \\ s_{41} & s_{42} & s_{43} & s_{44} & s_{45} \\ s_{51} & s_{52} & s_{53} & s_{54} & s_{55} \end{bmatrix} \begin{bmatrix} \hat{a}_1 \\ \hat{a}_2 \\ \hat{a}_3 \\ \hat{a}_4 \\ \hat{a}_5 \end{bmatrix} = \begin{bmatrix} \bar{x}_1^{(1)} - \bar{x}_1^{(2)} \\ \bar{x}_2^{(1)} - \bar{x}_2^{(2)} \\ \bar{x}_3^{(1)} - \bar{x}_3^{(2)} \\ \bar{x}_4^{(1)} - \bar{x}_4^{(2)} \\ \bar{x}_5^{(1)} - \bar{x}_5^{(2)} \end{bmatrix}.$$

Where $\bar{x}_j^{(k)}$ is the average of the j-th variable in class k, $s_{jj'}$ is the within covariance between the j-th and j'-th variables. They are evaluated by

$$\bar{x}_j^{(k)} = \frac{1}{n_k}\sum_{i=1}^{n_k} x_{ji}^{(k)}$$

$$s_{jj'} = \frac{1}{n_1 + n_2 - 2}\sum_{k=1}^{2}\sum_{i=1}^{n_k}(x_{ji}^{(k)} - \bar{x}_j^{(k)})(x_{j'i}^{(k)} - \bar{x}_{j'}^{(k)}).$$

S/W agreement rate

The S/W scoring algorithm was used to determine the S_{LC}/W_{LC} state from the activity intensity data in a total of 7078 epochs in the 31 subjects, and the agreement rate with the corresponding S_{PSG}/W_{PSG} results was calculated by subject and sleep stage. The agreement rate with the PSG-based sleep epochs (sensitivity) and agreement rate with the PSG-based wakefulness epochs (specificity) were also calculated by subject. SPSS version 11.5 was used for the statistical analysis (SPSS Japan Inc., Tokyo, Japan). Results were expressed as mean ± SD.

RESULTS

S/W scoring algorithm

The following S/W scoring algorithm was derived from the results of discriminant analysis of the activity

Table 1 Sleep parameters scored by polysomnography (PSG) and Lifecorder (LC) data

Sleep parameters	PSG	LC	Significance
Sleep efficiency (%)	90.2 ± 9.6 (61.8–99.1)	86.8 ± 11.1 (44.1–100.0)	$t(60) = 1.26$, $P = 0.21$
Total sleep time (min)	406.6 ± 78.9 (179.3–587.0)	376.3 ± 76.3 (208.0–586.0)	$t(60) = 1.53$, $P = 0.13$
Wake after sleep onset (min)	45.2 ± 48.3 (3.67–232.7)	59.9 ± 68.5 (0–388.0)	$t(60) = 0.98$, $P = 0.33$

Table 2 Decision parameters of S/W prediction algorithm for the Lifecorder

			Number of epochs
Agreement rates (%)	Overall	86.9 ± 8.9	7078
	Stage W	58.2 ± 30.4	819
	Stage 1	60.6 ± 26.2	427
	Stage 2	89.3 ± 10.6	3694
	Stage 3 + 4	99.2 ± 2.1	838
	Stage REM	90.1 ± 17.5	1300
Sensitivity (%)		89.4 ± 10.6	
Specificity (%)		58.2 ± 30.4	
Percentage of S_{PSG} epochs misscored as W_{LC} (%)		10.6 ± 10.6	
Percentage of W_{PSG} epochs misscored as S_{LC} (%)		41.8 ± 30.4	

S, sleep; W, wakefulness.

intensity data and PSG-based sleep/wake data from the total 7078 epochs obtained from 31 subjects:

$$z = 0.635x_1 + 0.427x_2 + 0.701x_3 + 0.805x_4 + 0.718x_5$$

where $z \geq 1$ indicates wakefulness (W_{LC}) and $z < 1$ indicates sleep (S_{LC}).

The linear discriminant function was transformed in advance by using linearity of the discriminant function in such a way that the threshold (z) becomes 1. Here, x_1, x_2, x_3, x_4, and x_5, indicate the activity intensity 4 min before the scored epoch, 2 min before the scored epoch, during the scored epoch, 2 min after the scored epoch, and 4 min after the scored epoch.

Validity of the S/W scoring algorithm

The sleep parameters derived from PSG and the LC activity intensity data are shown in Table 1. Sleep efficiency, total sleep time, and wakefulness after sleep onset were each derived from PSG and the LC activity intensity data (Table 1). No statistically significant differences were observed between PSG and the LC in any of the sleep parameters.

Table 2 shows the sleep/wake agreement rates between the LC and PSG, and the sensitivity and specificity of the LC. The overall agreement rate between the LC and PSG in the 31 subjects was 86.9 ± 8.9%. By sleep stage, the Stage 1 agreement rate was low at approximately 60%, but the Stage 2, Stage REM, and Stage 3 + 4 agreement rates were high at approximately 90% for Stage 2 and Stage REM and close to 100% for Stage 3 + 4.

The S/W scoring algorithm had a mean sensitivity (S detection) of 89.4 ± 10.6% and a mean specificity (W detection) of 58.2 ± 30.4%. In other words, 10.6 ± 10.6% of S_{PSG} were misscored as W_{LC} and 41.8 ± 30.4% of W_{PSG} were misscored as S_{LC}.

Activity intensity distribution before and after the scored epoch

Figure 1 shows the mean activity intensity recorded by the LC for nine consecutive epochs (18 min) centered at the W_{PSG} epoch (averaged for a total of W_{PSG} 819 epochs obtained from 31 subjects). The mean activity intensity recorded by the LC peaked just after the W_{PSG} epoch.

DISCUSSION

In the study, an S/W scoring algorithm for the LC was formulated through linear-based discriminant analysis of the corresponding longitudinal "PSG-based sleep/wake state" and "LC-recorded activity intensity" data in 7078 epoch recordings in 31 subjects over a total of

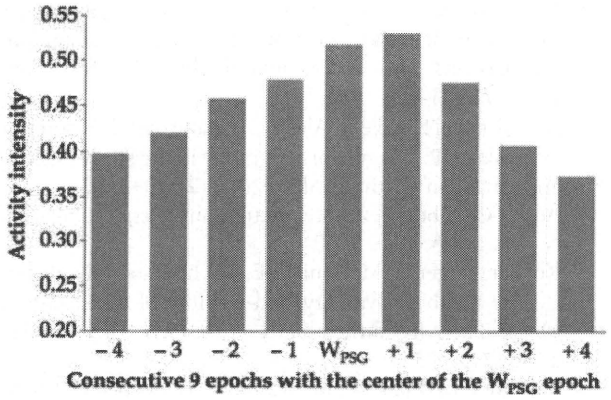

Figure 1 Activity intensity distribution before and after the scored epoch. The mean activity intensity recorded by the Lifecorder (LC) for nine consecutive epochs (18 min) centered at the W_{PSG} epoch. Vertical bars indicate the activity intensity. The mean activity intensity bars formed an inverted U-shape and peaked just after the W_{PSG} epoch.

235 h and 56 min. Comparison of the S/W activity determined from the LC data through the S/W scoring algorithm and the comparable activity determined from the PSG data through the rules of Rechtschaffen and Kales showed a mean agreement rate of approximately 87% in the 31 subjects. This rate is comparable to the 85 to 96% agreement rates obtained with conventional actigraphy units and their S/W scoring algorithms.[3–7] The LC and its S/W scoring algorithm yielded a high agreement rate of 90% or greater for Stage 2 and Stage 3 + 4 deep sleep and REM sleep, as well as an approximately 60% agreement rate for W_{PSG}, which is higher than that yielded by conventional algorithms. In order to examine the superiority of the five-dimensional model over the three-, seven-, or nine-dimensional models, we assumed linear models which incorporate the activity intensities during intervals of 6, 14, and 18 min centered at the time epoch of interest. The total agreement rates of the algorithms for the three-, five-seven-, and nine-dimensional models were 82.9%, 86.9% 86.0%, and 87.3%, respectively. Finally, we adopted the algorithm of the five-dimensional model since the agreement rate appeared to become saturated for models with more than five-dimensions. These findings show that when used with the S/W scoring algorithm developed in the study, the LC is a useful sleep assessment device with equivalent S/W identification capacity to conventional actigraphy systems.

Silent awakeness has been generally difficult to detect through actigraphic S/W assessment, in which it may be misscored as sleep, resulting in a pattern of overassessment of total sleep time and sleep efficiency compared to PSG-based assessment.[4,16,17] The LC and the S/W scoring algorithm derived in this study did not, however, result in a pattern of over-identification of S_{LC}, but contrarily yielded lower total sleep time and sleep efficiency values than the S_{PSG}/W_{PSG} assessment (Table 1). The specificity of the S/W scoring algorithm for the LC (58.2%) is in fact higher than that for conventional actigraphy units and their S/W scoring algorithms (40.6 *vs* 44%),[4,17] demonstrating that the S/W scoring algorithm for the LC developed in the study allows for more accurate identification of W_{LC}.

The S/W detection algorithm for wrist actigraphy used in a previous study assigned the highest weighting coefficient to the scored epoch.[4] However, in the S/W scoring algorithm for the LC, the highest weighting coefficient was assigned to the period immediately following the scored epoch. In fact, the mean activity intensity recorded by the LC peaked just after the W_{PSG} epoch (Fig. 1), and the delayed increase in truncal movement after awakening characterized the highest weighting coefficient assigned immediately after the scored epoch.

The LC is worn on the trunk while the conventional actigraphies used to be worn on the non-dominant wrist.[3–7] This may be related to the high specificity of the LC and its S/W scoring algorithm. The different application sites mean that S/W activity is assessed through different types of movement during sleep, either extremity or trunk movement (which are often independent),[18,19] which may produce the differences in assessment noted above. The LC and its S/W scoring algorithm investigated in the current study may more accurately detect silent awakeness due to the sensitivity to small movements of the torso during sleep and a resulting higher composite variable z value.

There are several issues that require further exploration with respect to use of the LC as a novel option for sleep assessment. First, the time epoch of S/W scoring algorithms for conventional actigraphy is often 1 min or less.[3,5,14] The time epoch for the LC used in this study is 2 min, leading to the assumption that devices with higher temporal resolution may result in higher agreement rates. Although it is more expensive (¥37 000 = €230 = $350), there is an LC that is programmable to 4-s time epochs. It would therefore be of merit to formulate an S/W scoring algorithm for this LC to determine whether it yields a higher agreement rate. Second, the S/W scoring algorithm formulated in the study uses the data from the scored time epoch as well as the data from the two epochs (4-min interval) immediately prior

and immediately after to scoring S/W. This means that activity intensity data prior to onset of sleep will be included in the scoring formula for the scored time epoch unless at least 4 min have passed from the onset of sleep on PSG. This complicates detection of differences in sleep latency of the order of several minutes. Accordingly, sleep latency was not analyzed in this study. This perhaps poses a constraint to the use of the LC in studies and tests requiring accurate evaluation of sleep latency. It is expected that development of LCs with higher temporal resolution and their S/W scoring algorithms will solve this issue.

In the current study, an S/W scoring algorithm for the LC was formulated from the data of young to middle-aged healthy adults and the validity of the algorithm was tested. Other potential useful applications of the inexpensive LC include sleep disorder screening in a large number of individuals. In the future, it will be necessary to determine whether the high agreement rates can also be obtained when the LC and its S/W scoring algorithm are used to assess sleep/wake activity in subjects from different age groups, including children and the elderly, and in patients with common sleep disorders, such as insomnia and sleep respiratory disturbances.

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Association between Depression and Insomnia Subtypes: A Longitudinal Study on the Elderly in Japan

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Study Objective: To examine the association between depression and three subtypes of insomnia, namely, difficulty initiating sleep (DIS), early morning awakening (EMA), and difficulty maintaining sleep (DMS).

Design: Cross-sectional and longitudinal study.

Setting: Community dwellers in Japan.

Participants: Nationally representative samples of adults aged 65 and over (total N = 4,997) were selected by a multistage stratified random sampling method in 1999 and were interviewed face-to-face in 1999, 2001, 2003, and 2006. Those who responded to the 3rd survey conducted in 2003 and the 4th survey conducted in 2006 were used in this study.

Measurement and Results: Depression was evaluated according to the 11-item short form of the CES-D scale at 2 points in time. Insomnia subtypes were assessed by self-reported measures. A logistic regression was employed to examine the association between insomnia subtypes and the presence of depression, controlling for relevant factors. A cross-sectional analysis based on the 2003 data demonstrated statistically significant odds ratios (ORs) for DIS and EMA. In the longitudinal study, DIS at the time of the 3rd survey was found to be significantly related to the presence of depression at the time of the 4th survey, with an odds ratio (95%CI) of 1.592 (1.012 to 2.504). EMA (OR 1.070; 95% CI, 0.664 to 1.723) and DMS (OR 1.215; 95% CI, 0.860 to 1.716), however, were not found to be significantly related to the presence of depression.

Conclusion: The longitudinal study revealed a statistically significant relationship, controlling for other relevant factors, between DIS and the presence of depression three years later, but not between EMA or DMS and depression. Based on our findings, we recommend that the association between insomnia subtypes and depression be studied longitudinally in clinical settings.

Keywords: Depression, insomnia subtypes, longitudinal study, elderly Japanese

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DEPRESSION IS SUSPECTED TO BE STRONGLY ASSOCIATED WITH SLEEPING DIFFICULTIES. THE WHO STUDY ON GLOBAL BURDEN OF DISEASES PREDICTED depression would be the second greatest Burden of Disease in 2020 in developed countries.[1] These countries therefore urgently need to address the issue of depression. Depression is prevalent among the aged, and it is known that its prevalence rises after the age of 50 among Japanese people.[2]

It is reported that insomnia can be a precursor or risk factor in depression and that depression could result in insomnia. Thus, the two diseases apparently have a bidirectional relationship.[3] Furthermore, insomnia is listed as a major diagnostic feature of depression in the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed (DSM-IV), attesting to the close association of the two diseases.[4]

This problem has attracted many researchers, and various epidemiological studies have thus far been carried out. In their pioneering longitudinal study, Ford and Kamerow[5] reported that those who complained of insomnia at the baseline showed a high risk of developing major depression after one year (odds ratio [OR]: 39.8), while those relieved of insomnia by the time of a second survey showed a much lower risk (OR: 1.6). Breslau et al.[6] observed young adults longitudinally for three years and found that those with a history of insomnia at the baseline had a relative risk of 4.0 of developing major depression by a second examination. Chang et al.[7] conducted a long-term cohort study in which they followed college graduates up to 45 years. They reported that insomnia in young people could result in the risk of developing depression for at least 30 years. All these studies have confirmed the importance of insomnia as a risk factor of depression and the need for early detection and treatment of insomnia. Riemann and Voderholzer[8] reviewed eight longitudinal studies (including the three studies mentioned above) conducted before 2000, which examined the relationship between depression and insomnia. In their review, they listed two other studies dealing with that relationship among those aged ≥ 65 years.[9,10] More recently, epidemiological longitudinal studies of the association between insomnia and depression were conducted in various populations: among those ≥ 18 years old in the UK,[11] those ≥ 30 years old in Norway,[12] young adults in Switzerland,[13] the general population in Sweden,[14] and those ≥ 65 years old in South Korea.[15] All of these studies, again, indicate the effect of insomnia on depression for different populations. These reports, however, did not examine the relationship of depression to the different insomnia subtypes: difficulty initiating sleep (DIS), early morning awakening (EMA), and difficulty maintaining sleep (DMS).

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